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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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R C van Dijk



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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
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Tetrahydroquinoline derivatives

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Tetrahydroquinoline derivatives

The invention relates to a compound having FSH receptor modulatory activity, in particular a tetrahydroquinoline derivative, to a pharmaceutical composition containing
5 the same, as well as the use of said compound in medical therapy.

Gonadotropins serve important functions in a variety of bodily functions including metabolism, temperature regulation and the reproductive process. Gonadotropins act on specific gonadal cell types to initiate ovarian and testicular differentiation and
10 steroidogenesis. The hypophyseal gonadotropin FSH (follicle stimulating hormone) for example plays a pivotal role in the stimulation of follicle development and maturation whereas LH (luteinizing hormone) induces ovulation (Sharp, R.M. Clin Endocrinol: 33:787-807, 1990; Dorrington and Armstrong, Recent Prog. Horm. Res. 35:301-342, 1979). Currently, FSH is applied clinically, in combination with LH or hCG, for
15 ovarian stimulation i.e. ovarian hyperstimulation for in vitro fertilisation (IVF) and induction of ovulation in infertile anovulatory women (Insler, V., Int. J. Fertility 33:85-97, 1988, Navot and Rosenwaks, J. Vitro Fert. Embryo Transfer 5:3-13, 1988), as well as for male hypogonadism and male infertility.

The gonadotropin FSH is released from the anterior pituitary under the influence of
20 gonadotropin-releasing hormone and oestrogens, and from the placenta during pregnancy. In the female, FSH acts on the ovaries promoting development of follicles and is the major hormone regulating secretion of oestrogens. In the male, FSH is responsible for the integrity of the seminiferous tubules and acts on Sertoli cells to support gametogenesis. Purified FSH is used clinically to treat infertility in females and
25 for some types of failure of spermatogenesis in males. Gonadotropins destined for therapeutic purposes can be isolated from human urine sources and are of low purity (Morse et al, Amer. J. Reproduct. Immunol. and Microbiology 17:143, 1988). Alternatively, they can be prepared as recombinant gonadotropins. Recombinant human FSH is available commercially and is being used in assisted reproduction
30 (Olijve et al. Mol. Hum. Reprod. 2:371, 1996; Devroey et al. Lancet 339:1170, 1992).

The actions of the FSH hormone are mediated by a specific plasma membrane receptor that is a member of the large family of G-protein coupled receptors. These receptors consist of a single polypeptide with seven transmembrane domains and are able to interact with the Gs protein, leading e.g. to the activation of adenylate cyclase.

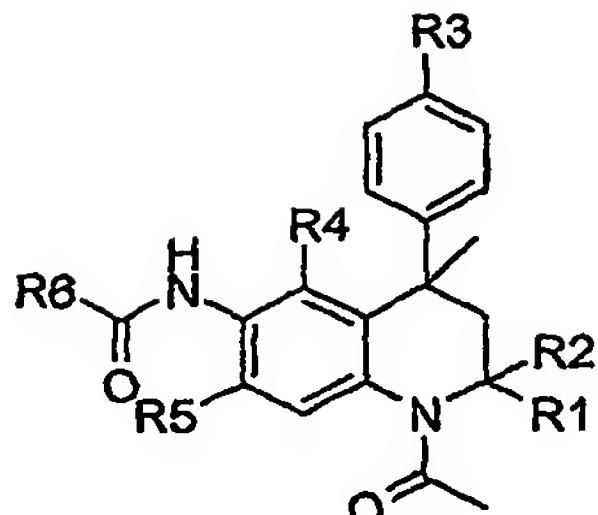
5 The FSH receptor is a highly specific target in the ovarian follicle growth process and is exclusively expressed in the ovary. Blocking this receptor or inhibiting the signaling which is normally induced after FSH-mediated receptor activation will disturb follicle development and thus ovulation and fertility. Low molecular weight FSH antagonists could therefore form the basis for new contraceptives. Such FSH antagonists could give rise to diminished follicle development (no ovulation) with still sufficient estrogen production left to avoid adverse effects on e.g. bone mass. On the other hand, 10 compounds that stimulate FSH receptor activity may serve to mimic the gonadotropic effect of the natural ligand.

15

The present invention describes the preparation of low molecular weight hormone analogs that selectively have modulatory activity on the FSH receptor. The compounds of the invention can either be used as (partial) agonists or (partial) antagonists of the FSH-receptor.

20

Thus, it has now been found, that the following class of tetrahydroquinoline compounds of formula I or pharmaceutically acceptable salts thereof, have FSH-modulatory activity:



Formula I

wherein

R¹ and R² are H or Me;

R³ is H, hydroxy, (1-4C)alkoxy, (di)(1-4C)alkylamino(2-4C)alkoxy or (2-

5 6)heterocycloalkyl(2-4C)alkoxy;

R⁴ is H, OH, (1-4C)alkoxy or R⁷;

R⁵ is H, OH, (1-4C)alkoxy or R⁷;

with the proviso that if R⁴ is H, R⁵ is not H, OH or (1-4C)alkoxy and that if R⁵ is H, R⁴ is not H, OH or (1-4C)alkoxy;

10 R⁶ is (2-5C)heteroaryl, (6C)aryl, (3-8C)cycloalkyl, (2-6C)heterocycloalkyl or (1-6C)alkyl;

R⁷ is amino, (di)(1-4C)alkylamino, (6C)arylcarbonylamino, (6C)arylcarbonyloxy, (2-5C)heteroarylcarbonylamino, (2-5C)heteroarylcarbonyloxy, R⁸-(2-4C)alkylamino, R⁸-(2-4C)alkoxy, R⁹-methylamino or R⁹-methoxy;

15 R⁸ is hydroxy, amino, (1-4C)alkoxy, (di)(1-4C)alkylamino, (2-6C)heterocycloalkyl, (2-6C)heterocycloalkylcarbonylamino, (di)(1-4C)alkylaminocarbonylamino or (1-4C)alkoxycarbonylamino and

R⁹ is aminocarbonyl, (di)(1-4C)alkylaminocarbonyl, (2-5C)heteroaryl or (6C)aryl.

20 R⁴ and R⁵ can independently be selected from each of the groups mentioned and need not be the same.

The compounds according to the present invention modulate the FSH receptor function and can be used for the same clinical purposes as native FSH if they behave like agonists, with the advantage that they display altered stability properties and may be

administered differently. If they block the FSH receptor they can be used e.g. as a contraceptive agent.

Thus, the FSH-receptor modulators of the present invention may be used for treating infertility, for contraception and for treatment of hormone-dependent disorders such as
5 breast cancer, prostate cancer, and endometriosis.

The following terms are intended to have the indicated meanings denoted below as used in the specification and claims.

The term (1-4C)alkyl as used herein means a branched or unbranched alkyl group
10 having 1-4 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl and tert-butyl.

The term (1-6C)alkyl as used herein means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl and hexyl. (1-5C)Alkyl groups are preferred, (1-4C)alkyl being the most
15 preferred.

The term (3-8C)cycloalkyl means a cycloalkyl group having 3-8 carbon atoms, being (3-cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. (3-6C)cycloalkyl groups are preferred.

The term (2-6C)heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and at least including one heteroatom selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom. Preferred heteroatoms are N or O. Most preferred are piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl.

The term (1-4C)alkoxy means an alkoxy group having 1-4 carbon atoms, the alkyl moiety having the same meaning as previously defined. (1-2C)Alkoxy groups are
25 preferred.

The term (2-4C)alkoxy means an alkoxy group having 2-4 carbon atoms, the alkyl moiety having the same meaning as previously defined.

The term (di)(1-4C)alkylamino as used herein means an amino group, monosubstituted or disubstituted with alkyl groups, each of which contain 1-4 carbon atoms and has the same meaning as previously defined.

The term (6C)aryl as used herein means a phenyl group, which may optionally be substituted with one or more substituents selected from hydroxy, amino, iodo, bromo, chloro, fluoro, nitro, trifluoromethyl, cyano, phenyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)(di)alkylamino, the alkyl, alkoxy and (di)alkylamino moieties having the same meaning as previously defined, for example phenyl, 3,5-dibromophenyl, 4-biphenyl, 3,5-dichlorophenyl, 3-bromo-6-methylamino-phenyl, 3-chloro-2,6-dimethoxyphenyl and 3,5-dimethylphenyl.

The term (2-5C)heteroaryl means a substituted or unsubstituted aromatic group having 2-5 carbon atoms, at least including one heteroatom selected from N, O and/or S, like imidazolyl, pyridyl, pyrimidyl, thienyl or furyl. The substituents on the heteroaryl group may be selected from the group of substituents listed for the (6C)aryl group. The heteroaryl group may be attached via a carbon atom or a heteroatom, if feasible. Preferred heteroaryl groups are thienyl, furyl and pyridyl.

The term di(1-4C)alkylamino(2-4C)alkoxy as used herein means a (di)alkylamino group, the alkyl moiety or alkyl moieties of which each contains 1-4 carbon atoms, connected via the amino group to the alkyl moiety of an alkoxy group having 2-4 carbon atoms, in which the (di)alkylamino group and the alkoxy group have the same meaning as previously defined.

The term (2-6C)heterocycloalkyl(2-4C)alkoxy as used herein means a heterocycloalkyl group having 2-6 carbon atoms, connected to the alkyl moiety of an alkoxy group having 2-4 carbon atoms, in which the alkoxy group and the heterocycloalkyl group have the same meaning as previously defined.

The term (6C)arylcarbonylamino as used herein means a phenyl group, optionally substituted with one or more substituents selected from the group of substituents listed for the (6C)aryl group, connected to the carbonyl moiety of a carbonylamino group, the (6C)aryl moiety having the same meaning as previously defined.

30 The term (6C)arylcarbonyloxy as used herein means a phenyl group, optionally substituted with one or more substituents selected from the group of substituents listed

for the (6C)aryl group, connected to the carbonyl moiety of a carbonyloxy group, the (6C)aryl moiety having the same meaning as previously defined.

The term (2-5C)heteroarylcarbonylamino as used herein means a heteroaryl group containing 2-5 carbon atoms, optionally substituted with one or more substituents selected from the group of substituents listed for the (6C)aryl group, connected to the carbonyl moiety of a carbonylamino group. The heteroaryl moiety in the heteroarylcarbonylamino group has the same meaning as previously defined.

The term (2-5C)heteroarylcarbonyloxy as used herein means a heteroaryl group containing 2-5 carbon atoms, optionally substituted with one or more substituents selected from the group of substituents listed for the (6C)aryl group, connected to the carbonyl moiety of a carbonyloxy group. The heteroaryl moiety in the heteroarylcarbonyloxy group has the same meaning as previously defined.

The term (2-6C)heterocycloalkylcarbonylamino as used herein means a heterocycloalkyl group having 2-6 carbon atoms, connected to the carbonyl moiety of a carbonylamino group, the heterocycloalkyl group having the same meaning as previously defined.

The term (di)(1-4C)alkylaminocarbonyl as used herein means a (di)alkylaminogroup, the alkyl group(s) of which having 1-4 carbon atoms, connected via the amino group to a carbonyl group, the (di)alkylamino group having the same meaning as previously defined.

The term (di)(1-4C)alkylaminocarbonylamino as used herein means a (di)alkylaminogroup, the alkyl group(s) of which having 1-4 carbon atoms, connected via the amino group to the carbonyl moiety of a carbonylamino group, thus providing a urea functionality, the (di)alkylamino group having the same meaning as previously defined.

The term (1-4C)alkoxycarbonylamino as used herein means an alkoxy group having 1-4 carbon atoms, attached to the carboyl moiety of a carbonylamino group, thus providing a carbamate functionality, the alkoxy group having the same meaning as previously defined

The term R⁸-(2-4C)alkylamino as used herein means a R⁸ group attached to the alkyl moiety of a (2-4C)alkylamino group, having the same meaning as previously defined.

The term R⁸-(2-4C)alkoxy as used herein means a R⁸ group attached to the alkyl moiety of a (2-4C) alkoxy group, having the same meaning as previously defined.

- 5 The term R⁹-methylamino as used herein means a R⁹ group attached to the methyl moiety of a methylamino group.

The term R⁹-methoxy as used herein means a R⁹ group attached to the methyl moiety of a methoxy group.

- The term pharmaceutically acceptable salt represents those salts which are, within the
10 scope of medical judgement, suitable for use in contact for the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. They may be obtained during the final isolation and purification of the compounds of the invention, or separately by reacting a free base
15 function, if present, with a suitable mineral acid such as hydrochloric acid, phosphoric acid, or sulfuric acid, or with an organic acid such as for example ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, methanesulfonic acid, and the like. If present, an acid function can be reacted with an organic or a mineral base, like sodium
20 hydroxide, potassium hydroxide or lithium hydroxide.

The invention thus relates to the compounds of Formula I as defined here above

In another embodiment the invention relates to compounds according to Formula I, wherein R³ is H, hydroxy or (1-4C)alkoxy.

- 25 The invention also relates to compounds of formula I, wherein R⁴ is H, OH or (1-4C)alkoxy.

In another embodiment the invention provides compounds of Formula I wherein R⁵ is OH, (1-4C)alkoxy or R⁷.

In another embodiment the invention provides compounds of Formula I wherein R⁶ is (2-5C)heteroaryl, (6C)aryl, (3-8C)cycloalkyl or (1-6C)alkyl.

In another aspect the invention relates to compounds according to Formula I wherein R⁶ is (2-5C)heteroaryl or (6C)aryl.

- 5 In still another aspect the heteroaryl group in R⁶ consists of 4 or 5 C atoms.

The invention also relates to compounds according to Formula I wherein R⁷ is (di)(1-4C)alkylamino, (2-5C)heteroarylcarbonylamino, (2-5C)heteroarylcarbonyloxy, R⁸-(2-4C)alkoxy, R⁹-methylamino or R⁹-methoxy.

- 10 Another aspect of the invention are compounds according to Formula I wherein R⁷ is (di)(1-4C)alkylamino, (2-5C)heteroarylcarbonyloxy, R⁸-(2-4C)alkoxy, R⁹-methylamino or R⁹-methoxy.

In still another aspect the invention relates to compounds according to Formula I wherein R⁷ is (di)(1-4C)alkylamino, R⁸-(2-4C)alkoxy, R⁹-methylamino or R⁹-methoxy.

- 15 In another aspect the invention relates to compounds according to Formula I wherein R⁸-(2-4C)alkoxy in R⁷ is R⁸-ethoxy.

In still another aspect the invention relates to compounds according to Formula I wherein R⁸-(2-4C)alkylamino in R⁷ is R⁸-ethylamino.

- 20 In another embodiment the invention provides compounds of Formula I wherein R⁸ is amino, (di)(1-4C)alkylamino, (2-6C)heterocycloalkyl, (2-6C)heterocycloalkylcarbonylamino or (1-4C)alkoxycarbonylamino.

In another embodiment the invention provides compounds of Formula I wherein R⁸ is amino, (di)(1-4C)alkylamino, (2-6C)heterocycloalkyl or (1-4C)alkoxycarbonylamino.

- 25 In yet another embodiment the invention provides compounds of Formula I wherein R⁸ is amino, (di)(1-4C)alkylamino, (2-6C)heterocycloalkyl or (2-6C)heterocycloalkylcarbonylamino.

The invention also relates to compounds according to Formula I wherein R⁸ is amino, (di)(1-4C)alkylamino or (2-6C)heterocycloalkyl.

- In yet another aspect of the invention R⁸ in the compounds of Formula I is (di)(1-4C)alkylamino or (2-6C)heterocycloalkyl.

In another aspect the invention relates to compounds according to Formula I wherein the heterocycloalkyl group in R^8 consists of 4 or 5 C atoms.

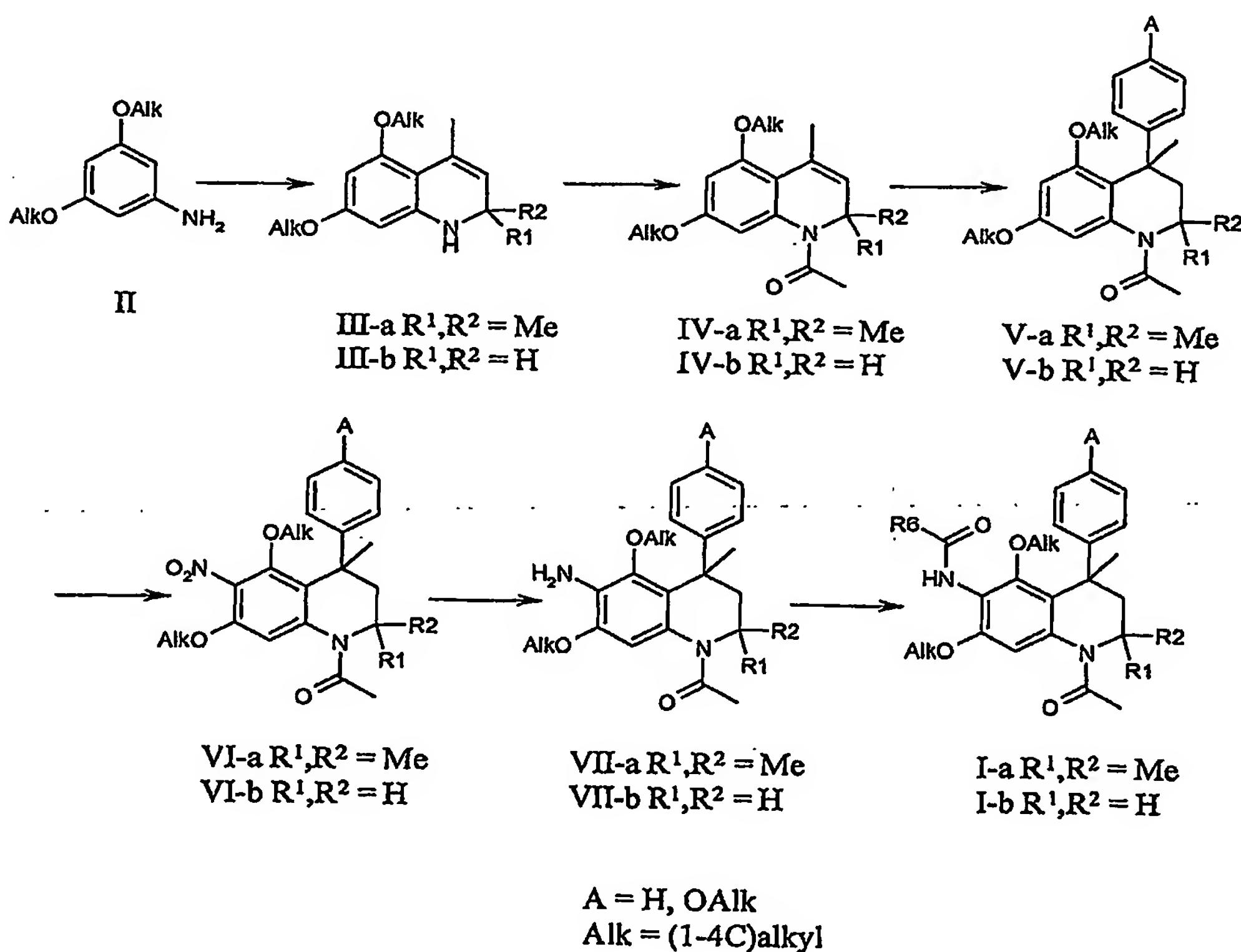
According to another embodiment of the invention R⁹ according to Formula I is aminocarbonyl, (2-5C)heteroaryl or (6C)aryl

- 5 According to yet another embodiment of the invention the heteroaryl group in R⁹ according to Formula I consists of 3, 4 or 5 C atoms.

Yet another aspect of the invention concerns compounds wherein all specific definitions of the groups R¹ through R⁹ as defined here above are combined in the compound of Formula I.

10

Suitable methods for the preparation of the compounds of the invention are outlined below.



The compounds of the present invention in which R⁴ and R⁵ are (1-4C)alkoxy, R¹ and R² are methyl and R⁶ is as previously defined can be prepared starting from appropriately substituted anilines of general formula II, by means of the well-documented Skraup reaction, which yields 2,2,4-trimethyl-1,2-dihydroquinoline derivatives of formula III-a.

Related Skraup cyclocondensations are found in literature: A. Knoevenagel, Chem. Ber. 54:1726, 1921; R.L. Atkins and D.E. Bliss, J. Org. Chem. 43:1975, 1978; J.V. Johnson, B.S. Rauckman, D.P. Baccanari and B. Roth, J. Med. Chem. 32:1942, 1989; W.C. Lin, S.-T. Huang and S.-T. Lin, J. Chin. Chem. Soc. 43:497, 1996; J.P. Edwards, 10 S.J. West, K.B. Marschke, D.E. Mais, M.M. Gottardis and T.K. Jones, J. Med. Chem. 41:303, 1998.

The abovementioned reaction is typically conducted at elevated temperature in acetone or mesityl oxide in the presence of iodine or protic acid such as hydrochloric acid, p-toluenesulfonic acid or aqueous hydrogen iodide. Alternatively, 1,2-dihydro-2,2,4-15 trimethylquinolines of formula III-a can be prepared by reacting the corresponding aniline of formula II with acetone in the presence of MgSO₄, 4-tert-butylcatechol and iodine (L.G. Hamann, R.I. Higuchi, L. Zhi, J.P. Edwards and X.-N. Wang, J. Med. Chem. 41:623, 1998). In yet another procedure, the reaction can be performed in acetone using lanthanide triflates (e.g. scandium triflate) as catalysts. In this case, the 20 reaction can be run at room temperature or at elevated temperatures using conventional heating or microwave irradiation (M. E. Theoclitou and L. A. Robinson, Tetrahedron Lett. 43:3907, 2002).

Starting materials can be either obtained directly from commercial sources or easily prepared by those skilled in the art.

25 Compounds of formula III-b can be prepared from anilines of general formula II by reaction with methyl vinyl ketone. Related cyclizations are described in United States Patent 2,686,182 (Badische Anilin- & Soda-Fabrik Aktiengesellschaft).

Subsequent 1-N-acetylation of compounds of formula III-a-b wherein R¹, and R² are as 30 previously defined, can be carried out using standard conditions. In a typical experiment, compounds of formula III are heated under reflux in acetic anhydride or reacted in a solvent such as dichloromethane, tetrahydrofuran, toluene or pyridine with

acetyl chloride in the presence of a base such as *N,N*-diisopropylethylamine, triethylamine or sodium hydride to give *N*-acetylated 4-methyl-1,2-dihydroquinoline derivatives of formula IV-a-b.

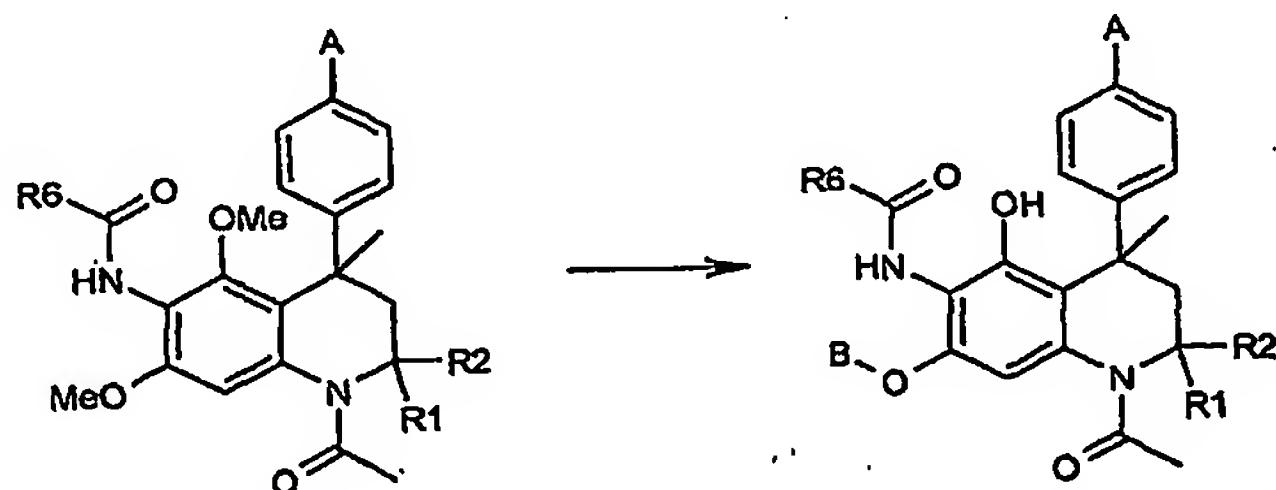
- Related *N*-acylations of a dihydroquinoline scaffold are found in literature: G.
5 Reddelien and A. Thurm, Chem. Ber. 65:1511, 1932; Zh. V. Shmyreva, Kh. S. Shikhaliev and E.B. Shpanig, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol. 31:45, 1988; Zh. V. Shmyreva, Kh. S. Shikhaliev, L.P. Zalukaev, Y.A. Ivanov, Y.S. Ryabokobylko and I.E. Pokrovskaya, Zh. Obshch. Khim. 59:1391, 1989.
- 10 Introduction of the requisite (substituted) phenyl group at position 4 of the dihydroquinoline scaffold can be accomplished via Friedel-Crafts alkylation of benzene or an appropriately substituted benzene with the compounds of general structure IV-a-b. This reaction is typically conducted at elevated temperatures either in neat benzene or the appropriately substituted benzene or in an appropriate inert solvent
15 such as heptane or hexane with benzene or the appropriately substituted benzene as reagent, under catalysis of a Lewis acid (e.g. AlCl₃, AlBr₃, FeCl₃ or SnCl₄). Friedel-Crafts alkylations with 2,2,4-trimethyl-1,2-dihydroquinolines are described in literature by B.A. Lugovik, L.G. Yudin and A.N. Kost, Dokl. Akad. Nauk SSSR, 170:340, 1966; B.A. Lugovik, L.G. Yudin, S.M. Vinogradova and A.N. Kost, Khim. Geterosikl. Soedin, 7:795, 1971.
- 20 Alternatively, anilines of general structure II can be reacted with an appropriately substituted 1-methylstyrene derivative and formaldehyde in acetonitrile at ambient or elevated temperature to give compounds of general structure V-b. Related cyclizations are described in literature: J.M. Mellor and G.D. Merriman, Tetrahedron, 51:6115,
25 1995.
- Compounds of general structure V-a-b can then be nitrated regioselectively at position 6 of the tetrahydroquinoline scaffold to give compounds of general structure VI-a-b. This reaction is typically conducted at temperatures in the range of -10 °C to room
30 temperature in dichloromethane using a mixture of nitric acid and acetic anhydride as a nitrating reagent. Alternatively, nitric acid can be added to a solution of the compounds

of general structure V-a-b in glacial acetic acid or in a mixture of acetic acid and dichloromethane. Related regioselective nitration of tetrahydroquinolines are described in literature: B. Golankiewicz, Pol. J. Chem., 54:355, 1980; Zh. V. Shmyreva, Kh. S. Shikhaliev, L.P. Zalukaev, Y.A. Ivanov, Y.S. Ryabokobylko and I.E. 5 Pokrovskaya, Zh. Obshch. Khim. 59:1391, 1989.

Reduction of the nitro group of the compounds of general structure VI-a-b can be accomplished by a large variety of methods well known in the art for the reduction of aromatic nitro compounds such as transition metal catalyzed hydrogenation, treatment 10 with sulfides, treatment with iron or other metals and (mild) acid, treatment with tin dichloride under acidic conditions and the like. More specifically, the reduction of the nitro group of the compounds of general formula VI-a-b can be accomplished by treatment with zinc dust and acetic acid in THF or 1,4-dioxane in the temperature range of 0 °C to 100 °C.

15

Subsequent 6-N-acylation of compounds of formula VII-a-b can be carried out using standard conditions, well known to those skilled in the art to give compounds of general structure I-a-b. For example, compounds of formula VII are reacted in a solvent such as dichloromethane, tetrahydrofuran, toluene or pyridine with an acyl 20 halide ($R^6-C(O)-Cl$) or acid anhydride ($R^6-C(O)-O-C(O)-R^6$) in the presence of a base



I-c $R^1, R^2 = Me$, A = OAlk, H
I-d $R^1, R^2 = H$, A = OAlk, H

I-e B = Me, A = OAlk, $R^1, R^2 = H, Me$
I-f B = Me, A = OH, $R^1, R^2 = H, Me$
I-g B = H, A = OH, $R^1, R^2 = H, Me$
I-h B = Me, A = H, $R^1, R^2 = H, Me$
I-i B = H, A = H, $R^1, R^2 = H, Me$

Alk = (1-4C)alkyl

such as *N,N*-diisopropylethylamine, triethylamine, pyridine or sodium hydride to give 6-*N*-acylated-1,2,3,4-tetrahydroquinoline derivatives of formula I-a-b. Alternatively, acylation of compounds of general formula VII-a-b to give compounds of general formula I-a-b can also be accomplished by reaction with an appropriate carboxylic acid (R⁶-CO₂H) in the presence of a coupling reagent such as *O*-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), *O*-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP) and a tertiary base, e.g. *N,N*-diisopropylethylamine, in a solvent such as *N,N*-dimethylformamide or dichloromethane at ambient or elevated temperature.

Compounds of the present invention wherein R³ = H, OH or (1-4C)alkoxy, R⁴ = OH, R⁵ = OH or (1-4C)alkoxy and R¹, R² and R⁶ are as previously described can be prepared by demethylation reactions of compounds of general formula I-c-d.

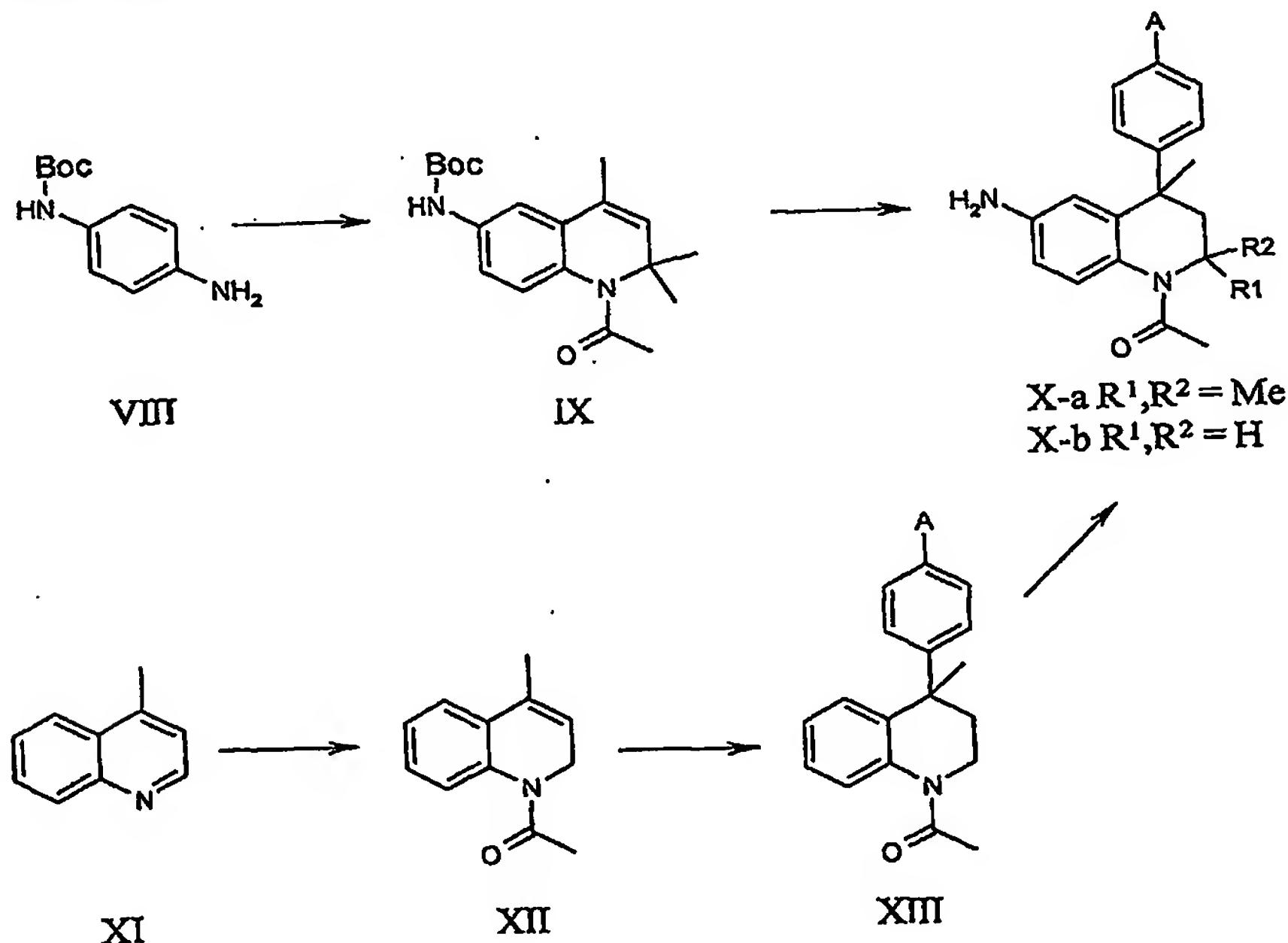
Demethylation reactions of aromatic methyl ethers are well known to those skilled in the art. In a typical experiment, demethylation is achieved upon reaction of a compound of formula I-c-d with BBr₃ in an inert solvent such as dichloromethane at low to ambient temperature to give demethylated compounds of general formula I-e-i. Alternatively, demethylation can be accomplished upon reaction of compounds of formula I-c-d with BF₃·Me₂S complex at ambient temperature. The degree of demethylation can be controlled to some extent by carefully controlling the reaction temperature and amount of the demethylating reagent. Generally, mixtures of mono-, di- and, if relevant, trihydroxy compounds of general formula I-e-i are obtained, which can be separated by chromatography. The demethylation reaction generally proceeds with a moderate degree of selectivity, with preferential demethylation at position 5 of the tetrahydroquinoline scaffold. The reaction rate for demethylation (dealkylation) of compounds of general formula I-c-d is 5-OMe > 4-(*p*-OAlk-phenyl) > 7-OMe.

Compounds of the present invention wherein R³ is H or a (functionalised) alkoxy group and R⁴ and/or R⁵ are (functionalised) alkoxy groups or acyloxy groups can be prepared by realkylation or acylation reactions of the hydroxyl groups of compounds of general

formula I-e-i with (functionalised) alkyl halides (e.g. chloroethylpyrrolidine) or acyl halides (e.g. 2-furoyl chloride or methyl chloroformate), respectively, under standard conditions.

- 5 The compounds of the present invention in which $R^4 = H$ and R^5 is connected to the tetrahydroquinoline scaffold via a nitrogen atom and R^1 , R^2 and R^6 are as previously defined can be prepared starting from *N*-Boc-1,4-phenylene diamine (VIII). The reaction sequence (a) Skraup reaction, (b) acetylation and (c) Friedel-Crafts alkylation of benzene or a substituted benzene as described before leads to the formation of 10 compounds of general formula X-a. It should be noted that the Boc-protective group is cleaved off under the reaction conditions of the Friedel-Crafts reaction.

Alternatively, *N*-Boc-1,4-phenylene diamine can be treated with methyl vinyl ketone, followed by acetylation and Friedel-Crafts reaction as described before to give compounds of general formula X-b.



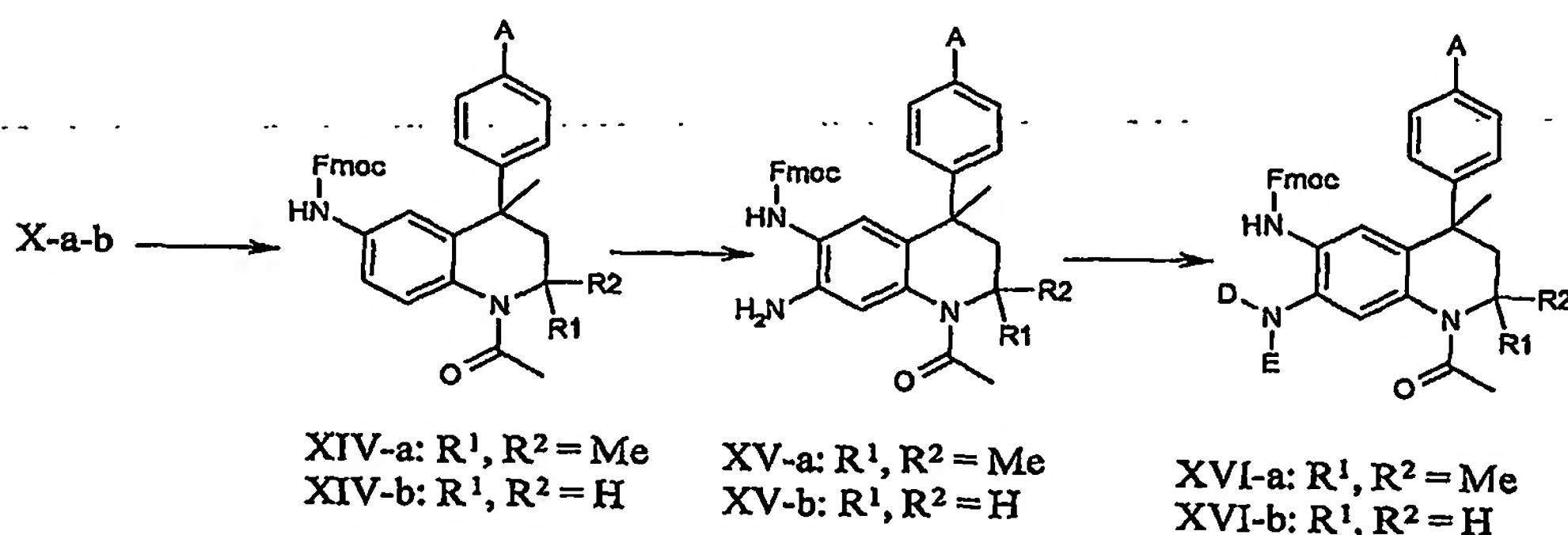
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In yet another procedure, compounds of general formula X-b can be obtained starting with the partial reduction of 4-methylquinoline (XI) with $BH_3 \cdot THF$ complex and

- sodium bis(2-methoxy-ethoxy)aluminum dihydride to give 4-methyl-1,2-dihydroquinoline, followed by acetylation as described before to give compound XII. Reductions of related quinolines to 1,2-dihydroquinolines are described in literature: see, for example: D. Roberts and J. A. Joule, *J. Org. Chem.* 62:568, 1997; R. F. Heier,
5 L. A. Dolak, J. N. Duncan, D. K. Hyslop, M. F. Lipton, I. J. Martin, M. A. Mauragis, M. F. Piercey, N. F. Nichols, P. J. K. D. Schreur, M. W. Smith and M. W. Moon, *J. Med. Chem.* 40: 639, 1997. Friedel-Crafts reaction of XII with benzene or an appropriately substituted benzene gives compounds of general formula XIII, which can be converted to compounds of general formula X-b by the regioselective 6-nitration
10 and reduction to the corresponding 6-amino derivative using previously described conditions. Regioselective nitration reactions on similar scaffolds have been reported in literature, see for example: Zh. V. Shmyreva et al., *J. Gen. Chem. USSR (Engl. Transl.)* 59: 1234, 1989.

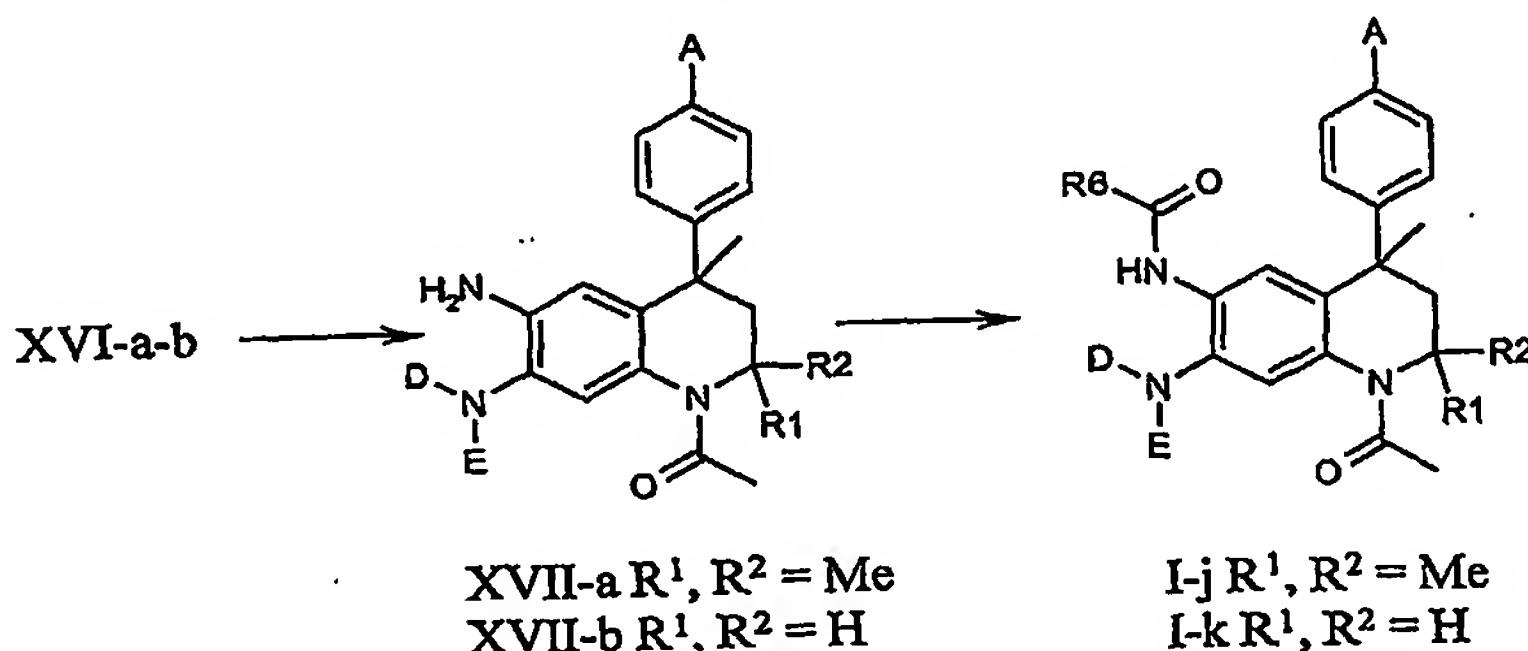
- 15 Compounds of general formula X-a-b can then be protected with the art known 9-fluorenylmethyloxycarbonyl group (Fmoc-group), see for example: T. W. Greene and P. M. Wuts, *Protective groups in organic synthesis* (3rd ed., John Wiley & Sons, Inc., 1999, see especially p. 506.). The abovementioned protection is conveniently carried out using FmocCl in THF with pyridine as a base.

20



Regioselective nitration at position 7 of the tetrahydroquinoline scaffold of compounds of general formula XIV-a-b, followed by reduction of the nitro group (*vide supra*),

gives 7-amino-1,2,3,4-tetrahydroquinoline derivatives of general formula XV-a-b. Regioselective nitration on related scaffolds with a similar substitution pattern can be found in literature; see, for example: S. H. Reich, M. A. M. Fuhr, D. Nguyen, M. J. Pino *et. al.*, *J. Med. Chem.* 35: 847, 1992; A. Ivobe, M. Uchida, K. Kamata, Y. Hotei, 5 H. Kusama, H. Harada, *Chem. Pharm. Bull.* 49: 822, 2001. The nitration conditions are similar to those described previously.



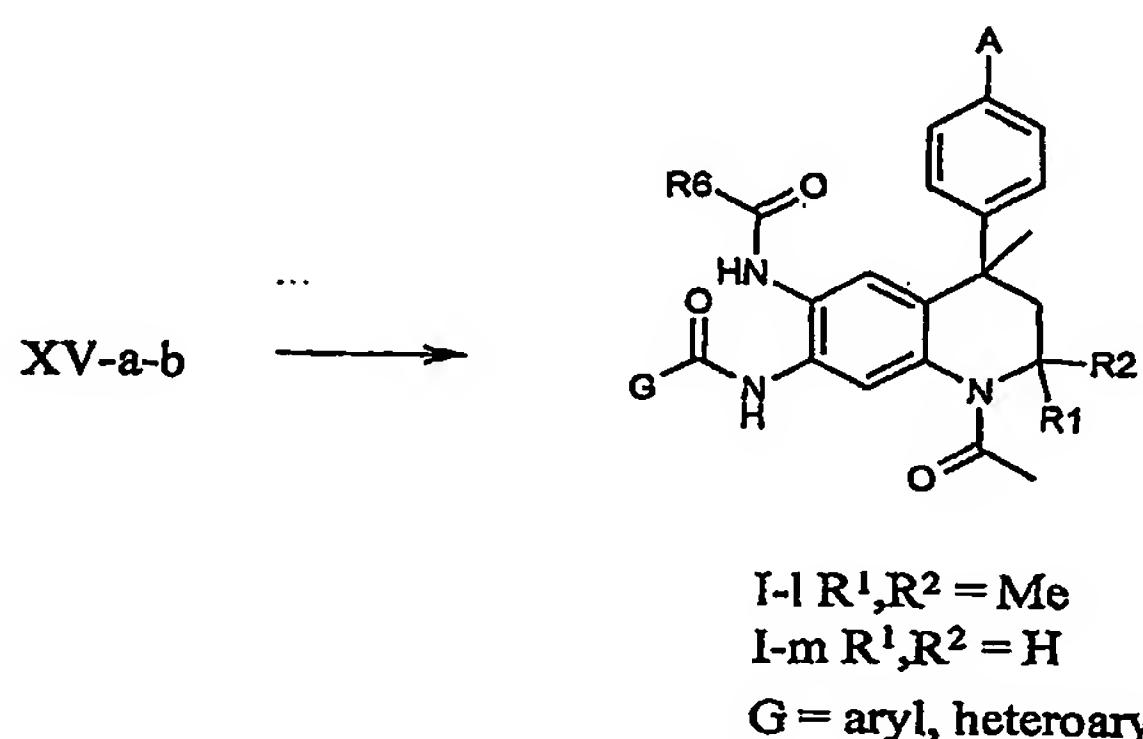
Reductive alkylation of the amino group at position 7 of tetrahydroquinoline derivatives of general formula XV-a-b using appropriately substituted aldehydes and a 10 suitable reducing agent (e.g. sodium cyanoborohydride or sodium triacetoxy borohydride) in a suitable solvent such as methanol or *N,N*-dimethylformamide leads to the formation of compounds of general formula XVIa-b. Generally, formaldehyde leads to the predominant formation of 7-dimethylamino tetrahydroquinoline derivatives (D = E = Me), whereas other aldehydes give rise to the predominant formation of 15 monoalkylated compounds of general formula XVIa-b (D = H, E = (functionalized) alkyl). Reductive alkylations of aromatic amines are well known to those skilled in the art.

Standard cleavage of the Fmoc protective group using piperidine in dichloromethane leads to 6-amino tetrahydroquinoline derivatives of general formula XVII-a-b which 20 can be acylated selectively at position 6 as described before to give compounds of the present invention of general formula I-j-k.

In another procedure, the amino group at position 7 of tetrahydroquinoline derivatives of general formula XV-a-b can be acylated with (hetero)aryl carboxylic acids (G-

CO₂H) or acyl chlorides (G-C(O)-Cl) as was described previously. In the subsequent steps, the same deprotection-acylation strategy (deprotection of 6-N-Fmoc and acylation of the resulting 6-NH₂) that was described previously then leads to compounds of the present invention of general formula I-l-m.

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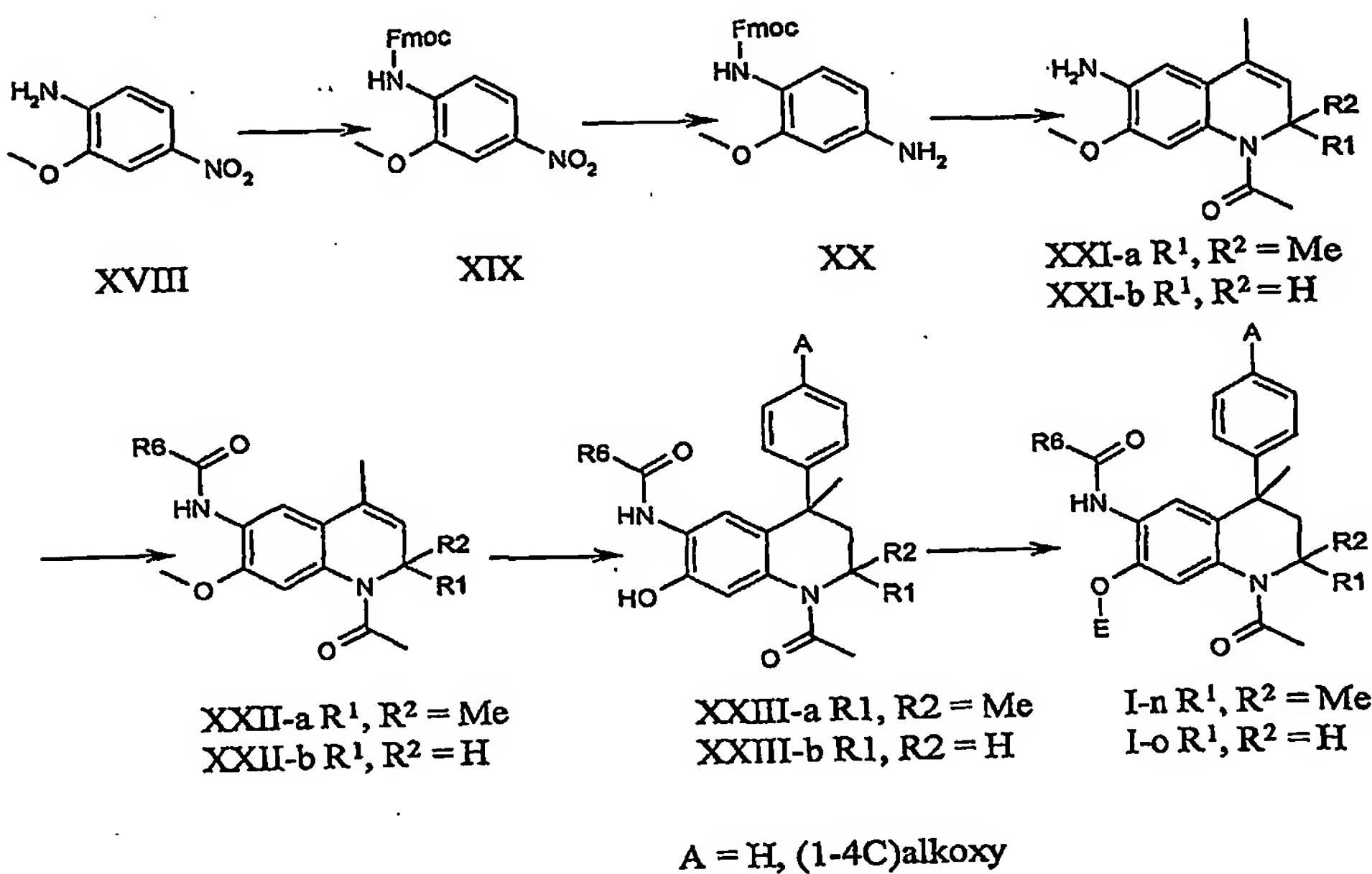


The compounds of the present invention in which R⁴ = H and R⁵ is connected to the tetrahydroquinoline scaffold via an oxygen atom and R¹, R² and R⁶ are as previously defined can be prepared starting from 2-methoxy-4-nitroaniline (XVII). The reaction sequence (a) Fmoc-protection to give XIX, (b) reduction of the nitro-group to give XX, followed by (c) regioselective Skraup reaction, (d) acetylation and (e) Fmoc-deprotection as described before leads to the formation of compounds of general formula XXI-a.

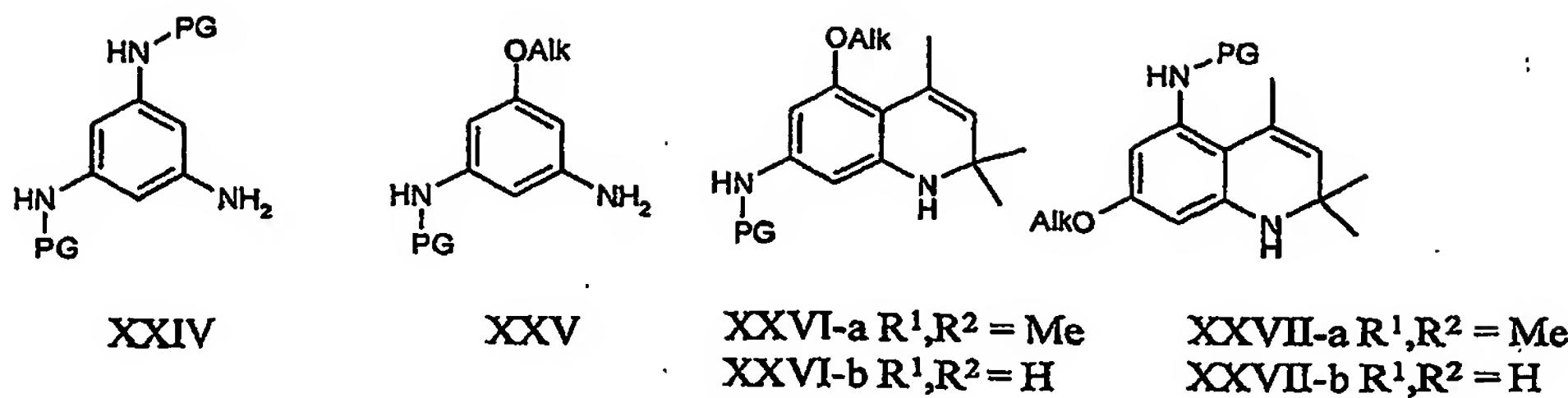
Compounds of general formula XXI-b may be obtained by treating compound XX with methyl vinyl ketone using the conditions described previously for the conversion of compounds of formula II to III-b, followed by 1-N-acetylation and Fmoc deprotection as described before.

Subsequent conversion of compounds of general formula XXI to XXIII may be effected by acylation of the 6-amino group using an appropriate acylating agent, for example acyl chloride R⁶-C(O)-Cl, followed by Friedel-Crafts reaction with benzene or an appropriate benzene derivative using conditions described previously. Under the Lewis-acidic conditions of the Friedel-Crafts reaction concomitant demethylation of the 7-OMe function in compounds of general formula XXII occurs. The thus obtained

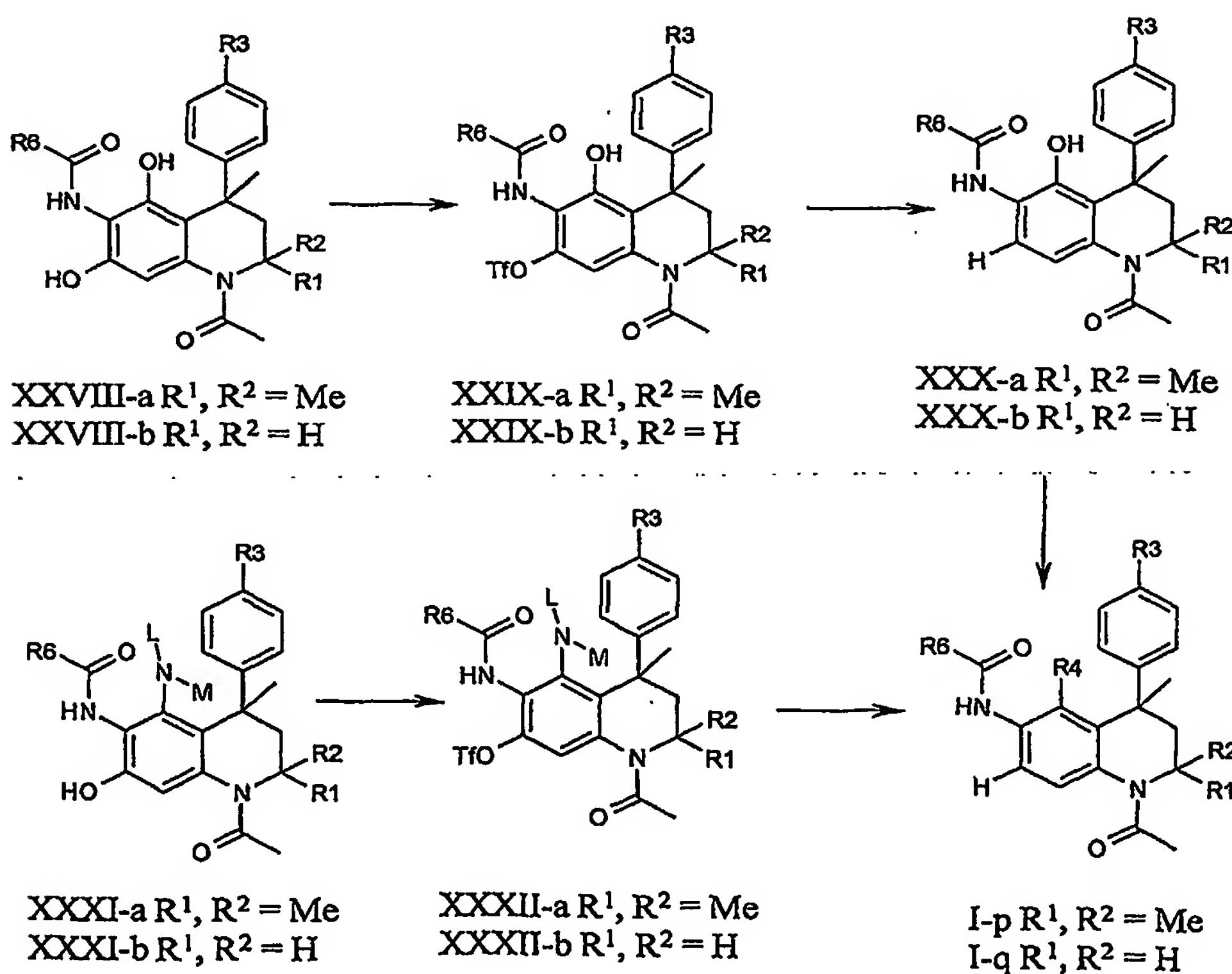
free 7-OH group in compounds of general formula XXIII may be realkylated or acylated with (functionalised) alkyl halides (e.g. chloroethylpyrrolidine) or acyl halides (e.g. 2-furoyl chloride or methyl chloroformate), respectively, under standard conditions to provide compounds of general formula I-n-o (E = functionalized alkyl, acyl or carbamate).



Compounds of the present invention in which R⁴ and R⁵ are connected via a nitrogen atom to the tetrahydroquinoline scaffold can be prepared from compounds of general formula XXIV, wherein PG is a nitrogen protective group, e.g. Boc, acetyl, methylcarbamate or Fmoc, via the previously described reactions e.g.: Skraup reaction or cyclocondensation with methyl vinyl ketone, 1-N-acetylation, cleavage of the protective group, N-alkylation, Friedel-Crafts reaction, nitration, nitro-reduction and acylation (*vide supra*).



Skraup reactions with acetone or mesityl oxide on compounds of general formula XXV may lead to two different regioisomeric products of general formula XXVI-a and XXVI-b, respectively. Conversion of compounds of general formula XXV using methyl vinyl ketone under previously described conditions may afford regioisomeric products with general formula XXVII-a en XXVII-b, respectively. Generally, these regioisomeric dihydroquinolines can be separated using chromatographical techniques (silicagel, HPLC) or crystallization and can subsequently be converted to compounds



of the current invention via the previously described routes.

Compounds of the present invention wherein $R^5 = H$ may be prepared by reductive 7-deoxygenation of compounds of general formula XXVIII or XXXI (L and/or M is appropriate (substituted) alkyl, acyl alkyloxycarbonyl or alkylaminocarbonyl) via 5 selective 7-O-triflation and subsequent reduction of the 7-OTf ($Tf =$ trifluoromethylsulfonyl) group. The requisite compounds of general formula XXXI are accessible from derivatives of general formula XXVII using previously described conditions. The (regioselective) triflation reaction may be effected under controlled 10 conditions using Tf_2N -phenyl and N,N -diisopropylethyl amine in DMF at room temperature. Generally, preferential triflation of the 7-OH group occurs. The subsequent reduction can be accomplished using a mixture of triphenyl phosphine, triethyl amine, formic acid and palladium(II) acetate as described in the literature. See for example K.A. Parker, Q. Ding, Tetrahedron 56:10249, 2000. Conversion of the 15 thus obtained compounds with general formula XXX or XXXII using previously described conditions then leads to compounds of general formula I-p-q, in which $R^5 = H$.

Some of the compounds of the invention, which can be in the form of a free base, may 20 be isolated from the reaction mixture in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salts may also be obtained by treating the free base of formula I with an organic or inorganic acid such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, maleic acid, malonic acid, methanesulphonic acid, fumaric acid, succinic 25 acid, tartaric acid, citric acid, benzoic acid, and ascorbic acid.

The compounds of the present invention possess at least one chiral carbon atom and, may therefore be obtained as pure enantiomers, or as a mixture of enantiomers, or as a mixture of diastereomers. Methods for obtaining the pure enantiomers are well known in the art, e.g crystallization of salts which are obtained from optically active acids and 30 the racemic mixture, or chromatography using chiral columns. For diastereomers, straight phase or reversed phase columns may be used.

The compounds of the invention may form hydrates or solvates. It is known to those of skill in the art that charged compounds form hydrated species when lyophilized with water, or form solvated species when concentrated in a solution with an appropriate organic solvent. The compounds of this invention include the hydrates or solvates of
5 the compounds listed.

For selecting active compounds testing at 10^{-5} M must result in an activity of more than 20% of the maximal activity when FSH is used as a reference. Another criterion might be the EC₅₀ value which must be $< 10^{-5}$ M, preferably $< 10^{-7}$ M.

- 10 The skilled artisan will recognize that desirable EC₅₀ values are dependent on the compound tested. For example, a compound with an EC₅₀ which is less than 10^{-5} M is generally considered a candidate for drug selection. Preferably this value is lower than 10^{-7} M. However, a compound which has a higher EC₅₀, but is selective for the particular receptor, may be even a better candidate.
- 15 Methods to determine receptor binding, as well as *in vitro* and *in vivo* assays to determine biological activity, of gonadotropins are well known. In general, the expressed receptor is contacted with the compound to be tested and binding or stimulation or inhibition of a functional response is measured.

To measure a functional response, isolated DNA encoding the FSH receptor gene,
20 preferably the human receptor, is expressed in suitable host cells. Such a cell might be the Chinese Hamster Ovary cell, but other cells are also suitable. Preferably the cells are of mammalian origin (Jia et al, Mol.Endocrin., 5:759-776, 1991).

- Methods to construct recombinant FSH expressing cell lines are well known in the art (Sambrook et al., Molecular Cloning: a Laboratory Manual, Cold Spring Harbor
25 Laboratory Press, Cold Spring Harbor, latest edition). Expression of receptor is attained by expression of the DNA encoding the desired protein. Techniques for site directed mutagenesis, ligation of additional sequences, PCR, and construction of suitable expression systems are all, by now, well known in the art. Portions, or all, of the DNA encoding the desired protein can be constructed synthetically using standard solid
30 phase techniques, preferably to include restriction sites for ease of ligation. Suitable control elements for transcription and translation of the included coding sequence can

be provided to the DNA coding sequences. As is well known, expression systems are now available which are compatible with a wide variety of hosts, including prokaryotic hosts such as bacteria and eukaryotic hosts such as yeast, plant cells, insect cells, mammalian cells, avian cells and the like.

- 5 Cells expressing the receptor are then contacted with the test compound to observe binding, or stimulation or inhibition of a functional response.

Alternatively, isolated cell membranes containing the expressed receptor may be used to measure binding of compound.

- 10 For measurement of binding, radioactively labeled or fluorescently labeled compounds may be used. Also competition binding assays can be performed.

Another assay involves screening for FSH receptor agonist compounds by determining stimulation of receptor mediated cAMP accumulation. Thus, such a method involves expression of the receptor on the cell surface of a host cell and exposing the cell to the test compound. The amount of cAMP is then measured. The level of cAMP can be reduced or increased, depending on the inhibitory or stimulating effect of the test compound upon binding to the receptor.

- 15
- 20 Screening for FSH receptor antagonists involves incubation of FSH receptor-expressing cells with a concentration range of the test compound in the presence of a fixed, submaximally effective, FSH concentration (i.e., a FSH concentration that induces approximately 80% of the maximal stimulation of cAMP accumulation in the absence of test compound). From the concentration-effect curves, the IC₅₀ value and the percentage of inhibition of FSH-induced cAMP accumulation can be determined for each of the test compounds.

- 25 In addition to direct measurement of e.g. cAMP levels in the exposed cell, cells lines can be used which in addition to transfection with receptor encoding DNA are also transfected with a second DNA encoding a reporter gene the expression of which responds to the level of cAMP. Such reporter genes might be cAMP inducible or might be constructed in such a way that they are connected to novel cAMP responsive elements. In general, reporter gene expression might be controlled by any response
- 30

element reacting to changing levels of cAMP. Suitable reporter genes are e.g. the genes encoding β -galactosidase, alkaline phosphatase, firefly luciferase and green fluorescence protein. The principles of such transactivation assays are well known in the art and are described e.g. in Stratowa, Ch., Himmeler, A. and Czernilofsky, A.P., 5 (1995) *Curr.Opin.Biotechnol.* 6:574. As reference compound human recombinant FSH can be used. In the alternative also competition assays can be performed

The present invention also relates to a pharmaceutical composition comprising a tetrahydroquinoline derivative or pharmaceutically acceptable salts thereof having the 10 general formula I in admixture with pharmaceutically acceptable auxiliaries and optionally other therapeutic agents. The auxiliaries must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

Compositions include e.g. those suitable for oral, sublingual, subcutaneous, 15 intravenous, intramuscular, local, or rectal administration, and the like, all in unit dosage forms for administration.

For oral administration, the active ingredient may be presented as discrete units, such as tablets, capsules, powders, granulates, solutions, suspensions, and the like.

For parenteral administration, the pharmaceutical composition of the invention may be 20 presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze-dried (lyophilized) condition requiring only the addition of sterile liquid carrier, e.g. water, prior to use.

Mixed with such pharmaceutically acceptable auxiliaries, e.g. as described in the 25 standard reference, Gennaro, A.R. et al., Remington: *The Science and Practice of Pharmacy* (20th Edition., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically acceptable liquids the active agent can be applied as a fluid 30 composition, e.g. as an injection preparation, in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

- For making solid dosage units, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the active agent of the invention
- 5 can be administered as solid compositions include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. For parenteral administration, aqueous suspensions, isotonic saline solutions and sterile injectable solutions may be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol.
- 10 The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition for the use as hereinbefore described.
- 15 The tetrahydroquinoline derivatives of the invention can also be administered in the form of implantable pharmaceutical devices, consisting of a core of active material, encased by a release rate-regulating membrane. Such implants are to be applied subcutaneously or locally, and will release the active ingredient at an approximately constant rate over relatively large periods of time, for instance from weeks to years.
- 20 Methods for the preparation of implantable pharmaceutical devices as such are known in the art, for example as described in European Patent 0,303,306 (AKZO Nobel N.V.).

The exact dose and regimen of administration of the active ingredient, or a pharmaceutical composition thereof, will necessarily be dependent upon the therapeutic effect to be achieved (treatment of infertility; contraception), and may vary with the particular compound, the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered.

In general parenteral administration requires lower dosages than other methods of administration which are more dependent upon absorption. However, a dosage for

30 humans preferably contains 0.0001-25 mg per kg body weight. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals

throughout the day, or, in case of female recipients, as doses to be administered at appropriate daily intervals throughout the menstrual cycle. The dosage as well as the regimen of administration may differ between a female and a male recipient.

- 5 Thus, the compounds according to the invention can be used in therapy.

A further aspect of the invention resides in the use of a tetrahydroquinoline derivative compound having the general formula I for the manufacture of a medicament to be used for the treatment of disorders responsive to FSH receptor mediated pathways. Thus, patients in need thereof can be administered with suitable amounts of the
10 compounds according to the invention.

In another aspect the invention resides in the use of a tetrahydroquinoline derivative compound having the general formula I for the manufacture of a medicament to be used for the control of fertility.

In yet another aspect the invention resides in the use of a tetrahydroquinoline derivative
15 compound having the general formula I for the manufacture of a medicament to be used for the treatment of infertility.

In still another aspect the invention resides in the use of a tetrahydroquinoline derivative compound having the general formula I for the manufacture of a medicament to be used to prevent fertility.

- 20 The compounds according to the invention can also be used for the treatment of hormone-dependent disorders such as breast cancer, prostate cancer and endometriosis.

The invention is illustrated by the following examples.

Examples

- 25 General Comments:

The following abbreviations are used in the examples: DMA = *N,N*-dimethylaniline, DIPEA = *N,N*-diisopropylethylamine, TFA = trifluoroacetic acid, DtBAD = di-*tert*-butyl azodicarboxylate, HATU = *O*-(7-azabenzotriazole-1-yl)-*N,N,N',N'*-

tetramethyluronium hexafluorophosphate, Fmoc = 9-fluorenylmethoxycarbonyl, Fmoc-Cl = 9-fluorenylmethoxycarbonylchloride, DMF = *N,N*-dimethylformamide, DMAP = 4-dimethylaminopyridine, THF = tetrahydrofuran.

Unless stated otherwise, all final products of the examples below are lyophilized from
5 water/1,4-dioxane mixtures or water/acetonitrile mixtures. If the compound was prepared as a HCl- or TFA salt, the respective acids were added in appropriate amounts to the solvent mixture before lyophilization.

The names of the final products described in the examples are generated using the Beilstein Autonom program (version: 2.02.119).

10 The following analytical HPLC methods are used for determination of retention times:

Method 1: Column: 5 μ m Luna C-18(2) 150 \times 4.6 mm; flow: 1ml/min; detection: 210 nm; column temperature: 40 °C; solvent A: CH₃CN/H₂O = 1/9 (v/v); solvent B: CH₃CN; solvent C: 0.1 M aqueous trifluoroacetic acid; gradient: solvent A/B/C = 65/30/5 to 10/85/5 (v/v/v) in 30.00 min, then constant for an additional 10.00 min at
15 A/B/C = 10/85/5 (v/v/v).

Method 2: Identical to method 1, except for the gradient used: Gradient: solvent A/B/C = 75/20/5 to 15/80/5 (v/v/v) in 30.00 min, then constant for an additional 10.00 min at A/B/C = 15/80/5 (v/v/v).

Method 3: Identical to method 1, except for the gradient used: Gradient: solvent A/B/C = 35/60/5 to 10/85/5 (v/v/v) in 30.00 min, then constant for an additional 10.00 min at
20 A/B/C = 10/85/5 (v/v/v).

Method 4: Column: 3 μ m Luna C-18(2) 100 \times 2 mm; flow: 0.25ml/min; detection: 210 nm; column temperature: 40 °C; solvent A: H₂O; solvent B: CH₃CN; gradient: solvent A/B = 75/25 to 0/100 (v/v) in 20.00 min, then constant for an additional 10.00 min at
25 A/B = 0/100 (v/v).

Method 5: Column: 3 μ m Luna C-18(2) 100 \times 2 mm; flow: 0.25ml/min; detection: 210 nm; column temperature: 40 °C; solvent A: H₂O; solvent B: CH₃CN; solvent C: 50 mM phosphate buffer, pH 2.1; gradient: solvent A/B/C = 70/20/10 to 10/80/10 (v/v/v) in 20.00 min, then constant for an additional 10.00 min at A/B/C = 10/80/10 (v/v/v).

30 Method 6: Identical to method 5, except for the gradient used: Gradient: solvent A/B/C = 65/30/5 to 10/85/5 (v/v/v) in 20.00 min, then constant for an additional 10.00 min at A/B/C = 10/85/5 (v/v/v).

The following methods are used for preparative HPLC-purifications:

Method A: Column = Luna C-18. Gradient: 0.1% trifluoroacetic acid in H₂O/CH₃CN (9/1, v/v)/CH₃CN = 80/20 to 0/100 (v/v) in 30–45 min, depending on the ease of separation. Detection: 210 nm.

Method B: Column = Luna C-18. Gradient: H₂O/CH₃CN (9/1, v/v)/CH₃CN = 80/20 to 5 0/100 (v/v) in 30–45 min, depending on the ease of separation. Detection: 210 nm.

Example 1

N-[1-Acetyl-5,7-dimethoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3-chloro-2,6-dimethoxy-benzamide

(a). 5,7-Dimethoxy-2,2,4-trimethyl-1,2-dihydroquinoline

10 A solution of 3,5-dimethoxyaniline (50 g) in acetone (800 ml) was added dropwise to a mixture of MgSO₄ (100 g) and Sc(OTf)₃ (8.0 g) in 1 l of acetone at room temperature. After 5 h another portion of Sc(OTf)₃ (3.2 g) was added and the reaction mixture was stirred until no starting material remained. After filtration, the acetone was partially evaporated in vacuo causing crystallization of the title compound which was collected 15 by filtration to yield 22 g after drying *in vacuo*. The remaining mother liquor was concentrated in vacuo and the residue was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent to give an additional 19.4 g of the title compound.

Yield: 42 g.

20

(b). 1-Acetyl-5,7-dimethoxy-2,2,4-trimethyl-1,2-dihydroquinoline

A mixture of the compound described in example 1a (42 g) and acetic anhydride (100 ml) was stirred at 100 °C for 20h. The reaction mixture was poured in 500 ml of ice-water while stirring. The precipitated solids were collected by filtration and dried *in vacuo* at 40 °C for 2 days. The remaining brown solid could be used crude for further 25 synthetic transformations.

Yield: 45 g.

(c). 1-Acetyl-5,7-dimethoxy-4-(4-methoxyphenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline

A mixture of the compound described in example 1b (30 g) and AlCl₃ (44 g) in anisole (500 ml) was stirred at 50°C for 18 h. The reaction mixture was cooled (0°C) and
5 quenched with water and ethyl acetate was added. The mixture was stirred overnight. The organic layer was separated, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was chromatographed on silicagel using heptane/ethyl acetate = 8/2 (v/v) as the eluent.

Yield: 15 g.

10

(d). 1-Acetyl-5,7-dimethoxy-4-(4-methoxyphenyl)-2,2,4-trimethyl-6-nitro-1,2,3,4-tetrahydroquinoline

A solution of acetic anhydride (450 µl) in fuming nitric acid (22.5 ml) was added dropwise to a solution of the compound described in example 1c (15 g) in CH₂Cl₂ (500 ml) at 0 °C. After complete addition the reaction mixture was stirred at room temperature for 3 h. Water was added and the organic layer was separated, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was crystallized from ethanol to give the title compound as a crystalline solid.

Yield: 10 g.

20

(e). 1-Acetyl-6-amino-5,7-dimethoxy-4-(4-methoxyphenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline

A solution of the compound described in example 1d (11.75 g) and acetic acid (15.5 ml) in THF (600 ml) was cooled to 0 °C. Zinc dust (36 g) was added in portions and the ice-bath removed. The temperature rose rapidly to 30 °C, after which the reaction mixture was allowed to cool down to room temperature. The excess of zinc was removed by filtration and to the filtrate was added CH₂Cl₂ and a saturated aqueous solution of Na₂CO₃. The organic layer was separated, dried over MgSO₄, filtered and concentrated *in vacuo*. The product was used crude in the next step.

30 Yield: 10.9 g.

(f). N-[1-Acetyl-5,7-dimethoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3-chloro-2,6-dimethoxy-benzamide

General procedure A: To a solution of the compound described in example 1e (100 mg), 3-chloro-2,6-dimethoxybenzoic acid (60 mg) and DIPEA (132 µl) in CH₂Cl₂ (2 ml) was added HATU (143 mg) at room temperature. If the reaction did not reach completion after 18 h, more HATU and DIPEA were added. After completion of the reaction a saturated aqueous solution of NaHCO₃ was added, the organic layer was separated, dried (MgSO₄) and concentrated *in vacuo*. The title compound was purified by preparative HPLC (method A).

Yield: 87 mg. MS-ESI: [M+H]⁺ = 597.4
HPLC: R_t = 17.98 min (method 1).

Example 2

4,5-Dimethyl-furan-2-carboxylic acid [1-acetyl-5,7-dimethoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

General procedure B: To a solution of the compound described in example 1e (800 mg), 4,5-dimethylfuran-2-carboxylic acid (308 mg) and DMA (768 µl) in DMF (10 ml) was added HATU (1.1 g) at room temperature. If the reaction did not reach completion after 18 h, the reaction mixture was heated to 50 °C. After completion of the reaction, water and ethyl acetate were added, the organic layer was separated, dried (MgSO₄) and concentrated *in vacuo*. The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

Yield: 444 mg. MS-ESI: [M+H]⁺ = 521.4
HPLC: R_t = 16.96 min (method 1).

Example 3

25 5-Bromo-thiophene-2-carboxylic acid [1-acetyl-5,7-dimethoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

According to general procedure B, the compound described in example 1e (800 mg), was acylated with 5-bromothiophene-2-carboxylic acid (456 mg), DMA (768 µl) and HATU (1.1 g) in CH₂Cl₂ (10 ml). The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

Yield: 1.0 g. MS-ESI: [M+H]⁺ = 589.2; HPLC: R_t = 18.90 min (method 2).

Example 4

Biphenyl-4-carboxylic acid [1-acetyl-5,7-dimethoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

General procedure C: To a solution of the compound described in example 1e (800 mg) and 4-biphenylcarbonyl chloride (475 mg) in CH_2Cl_2 (10 ml) was added DMA (768 μl) at room temperature. The reaction mixture was stirred until no starting material remained at which point water was added. The organic layer was separated, dried (MgSO_4) and concentrated *in vacuo*. The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

Yield: 678 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 579.4$; HPLC: $R_t = 26.19$ min (method 2).

Example 5

Furan-2-carboxylic acid [1-acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

(a). Furan-2-carboxylic acid [1-acetyl-5,7-dimethoxy-4-(4-methoxyphenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl]-amide

According to general procedure C, the compound described in example 1e (800 mg) was acylated with 2-furoyl chloride (217 μl) and DMA (768 μl) in CH_2Cl_2 (10 ml). The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

Yield: 896 mg

(b). Furan-2-carboxylic acid [1-acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

General procedure D: A solution of the compound described in example 5a (50 mg) in CH_2Cl_2 (4 ml) was cooled to -78°C , under an atmosphere of N_2 . Boron tribromide (28 μl) was added dropwise and after complete addition, the reaction mixture was allowed to slowly warm to room temperature. The reaction was quenched with water and CH_2Cl_2 was added. The organic layer was separated, dried (MgSO_4) and concentrated *in vacuo*. The title compound was purified by preparative HPLC (method A). Under the above described conditions, generally mixtures of compounds with a varying degree of demethylation are formed, which may be separated by preparative HPLC methods.

Yield: 9.1 mg; MS-ESI: $[\text{M}+\text{H}]^+ = 479.4$; HPLC: $R_t = 23.40$ min (method 2).

Example 6

N-[1-Acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dichloro-benzamide

- 5 (a). N-[1-Acetyl-5,7-dimethoxy-4-(4-methoxyphenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl]-3,5-dichlorobenzamide

According to general procedure C, the compound described in example 1e (800 mg) was acylated with 3,5-dichlorobenzoyl chloride (460 mg) and DMA (768 µl) in CH₂Cl₂ (10 ml). The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

10 Yield: 1.03 g

- (b). N-[1-Acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dichloro-benzamide

15 According to general procedure D, the compound described in example 6a (50 mg) was treated with boron tribromide (24 µl) in CH₂Cl₂ (4 ml). The title compound was purified by preparative HPLC. (method A).

Yield: 9.6 mg; MS-ESI: [M+H]⁺ = 557.2; HPLC: R_t = 23.40 min (method 2).

Example 7

5-Chloro-thiophene-2-carboxylic acid [1-acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

- 20 (a). 5-Chlorothiophene-2-carboxylic acid [1-acetyl-5,7-dimethoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl]-amide

25 According to general procedure B, the compound described in example 1e (800 mg) was acylated with 5-chlorothiophene-2-carboxylic acid (456 mg), DMA (768 µl) and HATU (1.1 g) in CH₂Cl₂ (10 ml). The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

Yield: 1.0 g

- (b). 5-Chloro-thiophene-2-carboxylic acid [1-acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

30 According to general procedure D, the compound described in example 7a (200 mg) was treated with boron tribromide (350 µl) in CH₂Cl₂ (25 ml) but in this case the temperature was not allowed to exceed -30 °C. The title compound was purified by

chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent, followed by preparative HPLC (method A).

Yield: 35 mg; MS-ESI: $[M+H]^+$ = 529.2; HPLC: R_t = 28.24 min (method 2).

Example 8

- 5 Biphenyl-4-carboxylic acid [1-acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

According to general procedure D, the compound described in example 4 (50 mg) was treated with boron tribromide (100 μ l) in CH_2Cl_2 (4 ml) but in this case the temperature was not allowed to exceed 0 °C. The reaction mixture also contains the product 10 described in example 10. The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

Yield: 43 mg; MS-ESI: $[M+H]^+$ = 565.4; HPLC: R_t = 32.53 min (method 2).

Example 9

- 15 Biphenyl-4-carboxylic acid [1-acetyl-5,7-dihydroxy-4-(4-hydroxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

According to general procedure D, the compound described in example 4 (50 mg) was treated with boron tribromide (100 μ l) in CH_2Cl_2 (4 ml) but in this case the temperature was allowed to reach 15 °C. The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

20 Yield: 33 mg; MS-ESI: $[M+H]^+$ = 537.4; HPLC: R_t = 24.16 min (method 2).

Example 10

- Biphenyl-4-carboxylic acid [1-acetyl-5-hydroxy-4-(4-hydroxy-phenyl)-7-methoxy-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

According to general procedure D, the compound described in example 4 (400 mg) was 25 treated with boron tribromide (800 μ l) in CH_2Cl_2 (25 ml) but in this case the temperature was not allowed to exceed 0 °C. The title compound (= a byproduct as described in example 8) was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

Yield: 50 mg; MS-ESI: $[M+H]^+$ = 551.4; HPLC: R_t = 27.58 min (method 2).

Example 11

4,5-Dimethyl-furan-2-carboxylic acid [1-acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

According to general procedure D, the compound described in example 2 (200 mg) was
5 treated with boron tribromide (336 µl) in CH₂Cl₂ (25 ml) but in this case the temperature was kept at -78 °C. The title compound was purified by preparative HPLC (method A).

Yield: 51 mg; MS-ESI: [M+H]⁺ = 507.4; HPLC: R_t = 24.32 min (method 1).

Example 12

10 N-[1-Acetyl-5-hydroxy-4-(4-hydroxy-phenyl)-7-methoxy-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dichloro-benzamide

According to general procedure D, the compound described in example 6a (75 mg) was treated with boron tribromide (38 µl) in CH₂Cl₂ (5 ml). The title compound was purified by preparative HPLC (method A).

15 Yield: 11 mg; MS-ESI: [M+H]⁺ = 543.4; HPLC: R_t = 25.66 min (method 2).

Example 13

N-[1-Acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dimethyl-benzamide

(a). N-[1-Acetyl-5,7-dimethoxy-4-(4-methoxyphenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl]-3,5-dimethyl-benzamide

According to general procedure B, the compound described in example 1e (800 mg), was acylated with 3,5-dimethylbenzoic acid (330 mg), DMA (768 µl) and HATU (1.1 g) in CH₂Cl₂ (10 ml). The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

25 Yield: 1.18 g

(b). N-[1-Acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dimethyl-benzamide

According to general procedure D, the compound described in example 13a (300 mg)
30 was treated with boron tribromide (513 µl) in CH₂Cl₂ (25 ml), but in this case the temperature was not allowed to exceed -40 °C. The title compound was purified by preparative HPLC (method A).

Yield: 41 mg; MS-ESI: $[M+H]^+$ = 517.4; HPLC: R_t = 13.89 min (method 3).

Example 14

N-[1-Acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dibromo-benzamide

- 5 (a). N-[1-Acetyl-5,7-dimethoxy-4-(4-methoxyphenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl]-3,5-dibromobenzamide

According to general procedure B, the compound described in example 1e (800 mg), was acylated with 3,5-dibromobenzoic acid (616 mg), DMA (768 μ l) and HATU (1.1 g) in DMF (10 ml). The title compound was purified by chromatography on silicagel 10 using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

Yield: 900 mg

(b). N-[1-Acetyl-5-hydroxy-7-methoxy-4-(4-methoxy-phenyl)-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dibromo-benzamide

- 15 According to general procedure D, the compound described in example 14a (300 mg) was treated with boron tribromide (639 μ l) in CH_2Cl_2 (25 ml), but in this case the temperature was not allowed to exceed -60 °C. The title compound was purified by preparative HPLC (method B).

Yield: 28 mg; MS-ESI: $[M+H]^+$ = 647.2; HPLC: R_t = 16.29 min (method 3).

20 **Example 15**

Biphenyl-4-carboxylic acid [1-acetyl-2,2,4-trimethyl-7-(2-morpholin-4-yl-ethoxy)-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

- (a). 1-Fmoc-2-methoxy-4-nitroaniline

A solution of 2-methoxy-4-nitroaniline (3.0 g) and pyridine (1.6 ml) in THF (30 ml) 25 was cooled to 0 °C. FmocCl (5.07 g) was added in portions and after complete addition the ice-bath was removed and the mixture was stirred for 5 h. The THF was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (175 ml). Methanol (ca 100 ml) was added and the CH_2Cl_2 was partly removed *in vacuo* until a precipitate formed. The mixture was allowed to stand for 1 h, after which time the crystals were collected by filtration 30 and dried *in vacuo* to give the title compound.

Yield: 6.32 g; MS-ESI: $[M+H]^+$ = 391.2

(b). 9-Fluorenylmethyl N-(2-methoxy-4-aminophenyl)carbamate

General procedure E: A mixture of the compound described in example 15a (6.07 g), acetic acid (8.9 ml) and THF (150 ml) was cooled to 0 °C. Zinc dust (20.4 g) was added in portions and the ice bath was removed. After the temperature slowly reached 10 °C it rapidly rose to 45 °C. After the reaction mixture was allowed to cool down to room temperature, the excess of zinc was removed by filtration and a large amount of CH₂Cl₂ (ca 500 ml) was added. The mixture was washed with saturated aqueous NaHCO₃ (3×200 ml) and brine (1×200 ml). The organic layer was separated, dried (MgSO₄), filtered and concentrated *in vacuo* until a precipitate formed. The mixture was allowed to stand overnight at 0 °C, after which time the crystals were collected by filtration and dried *in vacuo* to give the title compound.

Yield: 4.45 g.

15 (c). (7-Methoxy-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester

A mixture of the compound described in example 15b (4.45 g), I₂ (157 mg), MgSO₄ (7.4 g), 4-*tert*-butylcatechol (61 mg) and acetone (ca 350 ml) was heated at reflux for 5 h. The MgSO₄ was removed by filtration and the filtrate was concentrated *in vacuo*.
20 The title compound was obtained by chromatography on silicagel using heptane/ethyl acetate = 9/1 => 7/3 (v/v) as the eluent.

Yield: 4.24 g.

25 (d). (1-Acetyl-7-methoxy-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester

To a solution of the compound described in example 15c (4.24 g) in pyridine (25 ml) and CH₂Cl₂ (25 ml) was added a small amount of DMAP (ca 20 mg). Acetyl chloride (2.0 ml) in CH₂Cl₂ (20 ml) was slowly added. After complete addition the mixture was diluted with CH₂Cl₂ (ca 100 ml) and washed with water (3×100 ml), 0.1 M aq HCl (3×100 ml), 0.5 M aq HCl (1×100 ml) and brine (1×100 ml). The organic layer was dried (MgSO₄) and concentrated *in vacuo*. The title compound was obtained by chromatography on silicagel using heptane/ethyl acetate = 9/1 => 7/3 (v/v) as the eluent.

Yield: 3.91 g.

(e). 1-Acetyl-6-amino-7-methoxy-2,2,4-trimethyl-1,2-dihydroquinoline

Piperidine (8.0 ml) was added to a solution of the compound described in example 15d
5 (3.91 g) in CH₂Cl₂ (80 ml). After 1.5 h, the reaction mixture was concentrated *in vacuo* and the title compound was obtained by chromatography on silicagel using heptane/ethyl acetate = 9/1 => 7/3 (v/v) as the eluent.

Yield: 2.2 g

10 (f). Biphenyl-4-carboxylic acid (1-acetyl-7-methoxy-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)-amide

General procedure F: To a mixture of the compound described in example 15e (2.2 g), toluene (45 ml) and pyridine (5 ml) was added 4-biphenylcarbonyl chloride (2.21 g). If the reaction did not reach completion after 3 h at room temperature, an additional portion of 4-biphenylcarbonyl chloride (2.0 g) was added. Stirring was continued for 15 30 min, after which the reaction mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (ca 100 ml) and washed with saturated aq NaHCO₃ (100 ml), 1 M aq HCl (3×100 ml) and brine (100 ml). The organic layer was dried (MgSO₄) and concentrated *in vacuo*. To the residue was added CH₂Cl₂ (ca 50 ml) and the solids were 20 removed by filtration and discarded. The filtrate was concentrated *in vacuo* and the title compound was obtained by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 1/1 (v/v) as the eluent.

Yield: 3.1 g.

25 (g). Biphenyl-4-carboxylic acid (1-acetyl-7-hydroxy-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-amide

General procedure G: To a solution of the compound described in example 15f (3.1 g) in benzene (100 ml) was added aluminum trichloride (5.6 g) and the reaction mixture was stirred for 20 h at room temperature. The reaction was quenched with H₂O (ca 100 ml) and the pH of the mixture was adjusted to pH 8 with 2 M aq NaOH while stirring vigorously. Ethyl acetate (ca 300 ml) was added and the organic layer was 30 washed with H₂O (2×150 ml) and brine (1×150 ml), dried (MgSO₄) and concentrated *in vacuo* to yield the product that was used without further purification.

Yield: 3.5 g.

(h). Biphenyl-4-carboxylic acid [1-acetyl-2,2,4-trimethyl-7-(2-morpholin-4-yl-ethoxy)-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

5 **General procedure H:** A mixture of the compound described in example 15g (70 mg), *N*-(2-chloroethyl)-morpholine hydrochloride (31 mg), Cs₂CO₃ and DMF (3 ml) was stirred at 50 °C, until no starting material remained. The reaction mixture was diluted with ethyl acetate (15 ml) and water was added (ca 15 ml). The organic layer was washed with water (3×15 ml), separated, dried (MgSO₄), filtered and concentrated *in vacuo*. The title compound was obtained as the corresponding HCl salt by lyophilization from a mixture of 1,4-dioxane and H₂O containing HCl.

10 Yield: 63 mg (HCl salt); MS-ESI: [M+H]⁺ = 618.6; HPLC: R_t = 19.49 min (method 4).

Example 16

15 Biphenyl-4-carboxylic acid (1-acetyl-7-dimethylcarbamoylmethoxy-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

According to general procedure H, the compound described in example 15g (79 mg) was alkylated with 2-chloro-*N,N*-dimethylacetamide (23 mg) and Cs₂CO₃ (255 mg) in DMF (2 ml). The title compound was purified by crystallization from CH₃CN.

Yield: 15 mg; MS-ESI: [M+H]⁺ = 590.6; HPLC: R_t = 23.58 min (method 5).

20 **Example 17**

Biphenyl-4-carboxylic acid [1-acetyl-2,2,4-trimethyl-4-phenyl-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

According to general procedure H, the compound described in example 15g (79 mg) was alkylated with *N*-(3-chloropropyl)piperidine hydrochloride (37.4 mg) and Cs₂CO₃ (255 mg) in DMF (2 ml). The title compound was purified by crystallization from CH₃CN.

25 Yield: 83 mg (HCl salt); MS-ESI: [M+H]⁺ = 630.8; HPLC: R_t = 15.49 min (method 5).

Example 18

Biphenyl-4-carboxylic acid [1-acetyl-2,2,4-trimethyl-4-phenyl-7-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

According to general procedure H, the compound described in example 15g (79 mg) was alkylated with 2-picoly l chloride hydrochloride (31 mg) and Cs₂CO₃ (255 mg) in DMF (2 ml). The title compound was purified by crystallization from CH₃CN.

Yield: 32 mg (HCl salt); MS-ESI: [M+H]⁺ = 596.6; HPLC: R_t = 22.41 min (method 6).

Example 19

Biphenyl-4-carboxylic acid [1-acetyl-2,2,4-trimethyl-4-phenyl-7-(pyridin-3-ylmethoxy)-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

According to general procedure H, the compound described in example 15g (79 mg) was alkylated with 3-picoly l chloride hydrochloride (31 mg) and Cs₂CO₃ (255 mg) in DMF (2 ml). The title compound was purified by crystallization from CH₃CN.

Yield: 36 mg (HCl salt); MS-ESI: [M+H]⁺ = 596.6; HPLC: R_t = 19.70 min (method 6).

Example 20

Biphenyl-4-carboxylic acid [1-acetyl-2,2,4-trimethyl-4-phenyl-7-(pyridin-4-ylmethoxy)-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

According to general procedure H, the compound described in example 15g (79 mg) was alkylated with 4-picoly l chloride hydrochloride (31 mg) and Cs₂CO₃ (255 mg) in DMF (2 ml). The title compound was purified by crystallization from CH₃CN

Yield: 31 mg (HCl salt); MS-ESI: [M+H]⁺ = 596.4; HPLC: R_t = 17.09 min (method 6).

Example 21

Biphenyl-4-carboxylic acid [1-acetyl-7-(2-dimethylamino-ethoxy)-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl]-amide

According to general procedure H, the compound described in example 15g (79 mg) was alkylated with 2-dimethylaminoethylchloride hydrochloride (27 mg) and Cs₂CO₃ (255 mg) in DMF (2 ml). The title compound was purified by crystallization from CH₃CN.

Yield: 55 mg (HCl salt); MS-ESI: [M+H]⁺ = 576.6; HPLC: R_t = 14.94 min (method 5).

Example 22

Biphenyl-4-carboxylic acid (1-acetyl-7-carbamoylmethoxy-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

According to general procedure H, the compound described in example 15g (79 mg) was alkylated with 2-chloroacetamide (18 mg) and Cs₂CO₃ (255 mg) in DMF (2 ml). The title compound was purified by preparative HPLC (method A).

Yield: 60.2 mg; MS-ESI: [M+H]⁺ = 562.4; HPLC: R_t = 20.47 min (method 5).

Example 23

Morpholine-4-carboxylic acid (3-{1-acetyl-6-[(biphenyl-4-carbonyl)-amino]-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-7-yloxy}-propyl)-amide

According to general procedure H, the compound described in example 15g (79 mg) was alkylated with morpholine-4-carboxylic acid (3-chloropropyl)amide (40 mg) and Cs₂CO₃ (255 mg) in DMF (2 ml). The title compound was purified by preparative HPLC (method A).

Yield: 52.4 mg; MS-ESI: [M+H]⁺ = 675.6; HPLC: R_t = 22.31 min (method 5).

Example 24

Furan-2-carboxylic acid 1-acetyl-6-(3,5-dibromo-benzoylamino)-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-7-yl ester

(a). N-(1-Acetyl-7-methoxy-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)-3,5-dibromo-benzamide

According to general procedure F, the compound described in example 15e (1.0 g) was acylated with 3,5-dibromobenzoyl chloride (1.72 g) in toluene (9 ml) and pyridine (1 ml). The title compound was obtained by chromatography on silicagel using heptane/ethyl acetate = 8/2 (v/v) as the eluent.

Yield: 1.3 g

(b). N-(1-Acetyl-7-hydroxy-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-3,5-dibromo-benzamide

According to general procedure G, the compound described in example 24a (1.3 g) was stirred with AlCl₃ (1.0 g) in benzene (50 ml). The product obtained was used without further purification.

Yield: 1.39 g

(c). Furan-2-carboxylic acid 1-acetyl-6-(3,5-dibromo-benzoylamino)-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-7-yl ester

- 5 A mixture of the compound described in example 24b (100 mg), furoyl chloride (16 μ l) and DIPEA (60 μ l) and CH_2Cl_2 (5 ml) was stirred at room temperature until no starting material remained. Water was added and the organic layer was separated, washed with brine, dried (MgSO_4) and concentrated *in vacuo*. The title compound was purified by preparative HPLC (method A).
- 10 Yield: 47 mg; MS-ESI: $[\text{M}+\text{H}]^+ = 681.2$; HPLC: $R_t = 31.6$ min (method 2).

Example 25

N -[1-Acetyl-7-(2-amino-ethoxy)-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dibromo-benzamide

- General procedure I:** A mixture of the compound described in example 24b (100 mg),
15 *tert*-butyl N -(2-hydroxyethyl)carbamate (29 mg), DtBAD (79 mg), DIPEA (60 μ l) and
an excess of polymer bound triphenylphosphine in CH_2Cl_2 (5 ml) was stirred at room
temperature until no starting material remained. The reaction mixture was filtered and
washed with water and brine. The organic layer was separated, dried (MgSO_4) and
concentrated *in vacuo*. The crude product was taken up in CH_3CN (ca 1 ml) and a few
20 drops of TFA were added facilitating cleavage of the *tert*-butylcarbamate. The title
compound was purified by preparative HPLC (method A).

Yield: 17 mg (TFA salt); MS-ESI: $[\text{M}+\text{H}]^+ = 630.2$; HPLC: $R_t = 15.6$ min (method 2).

Example 26

{2-[1-Acetyl-6-(3,5-dimethyl-benzoylamino)-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-ethyl}-carbamic acid *tert*-butyl ester

- (a). N -(1-Acetyl-7-methoxy-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)-3,5-dimethyl-benzamide

According to general procedure F, the compound described in example 15e (1.0 g) was
acylated with 3,5-dimethylbenzoyl chloride (0.97 g) in toluene (9 ml) and pyridine (1
30 ml). The title compound was obtained by chromatography on silicagel using
heptane/ethyl acetate = 8/2 (v/v) as the eluent.

Yield: 1.1 g

(b). N-(1-Acetyl-7-hydroxy-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-3,5-dimethylbenzamide

According to general procedure G, the compound described in example 26a (1.1 g) was
5 stirred with AlCl₃ (1.0 g) in benzene (50 ml). The product obtained was used without further purification.

Yield: 1.3 g

10 (c). {2-[1-Acetyl-6-(3,5-dimethyl-benzoylamino)-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-ethyl}-carbamic acid *tert*-butyl ester

According to general procedure I, the compound described in example 26b (100 mg) was alkylated with *tert*-butyl N-(2-hydroxyethyl)carbamate (37 mg), DtBAD (101 mg), DIPEA (77 µl) and an excess of polymer bound triphenylphosphine in CH₂Cl₂ (5 ml). In this case the the *tert*-butylcarbamate was not cleaved, affording the title product after 15 preparative HPLC (method A) and lyophilization.

Yield: 38 mg; MS-ESI: [M+H]⁺ = 600.4; HPLC: R_t = 33.1 min (method 2).

Example 27

N-[1-Acetyl-7-(furan-2-ylmethoxy)-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dimethyl-benzamide

20 According to general procedure I, the compound described in example 26b (100 mg) was alkylated with 2-(hydroxymethyl)furan (21 µl), DtBAD (101 mg), DIPEA (77 µl) and an excess of polymer bound triphenylphosphine in CH₂Cl₂ (5 ml). The title product was purified by preparative HPLC (method A), followed by lyophilization.

Yield: 16 mg; MS-ESI: [M+H]⁺ = 537.4; HPLC: R_t = 32.8 min (method 2).

25 **Example 28**

N-[1-Acetyl-2,2,4-trimethyl-4-phenyl-7-(pyridin-4-ylmethoxy)-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dichloro-benzamide

(a). N-(1-Acetyl-7-methoxy-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)-3,5-dichloro-benzamide

30 According to general procedure F, the compound described in example 15e (1.0 g) was acylated with 3,5-dichlorobenzoyl chloride (1.2 g) in toluene (9 ml) and pyridine (1

ml). The title compound was obtained by chromatography on silicagel using heptane/ethyl acetate = 8/2 (v/v) as the eluent.

Yield: 1.47 g

5 (b). N-(1-Acetyl-7-hydroxy-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-3,5-dichlorobenzamide

According to general procedure G, the compound described in example 28a (1.47 g) was stirred with AlCl₃ (1.5 g) in benzene (75 ml). The product obtained was used without further purification.

10 Yield: 1.51 g

(c). N-[1-Acetyl-2,2,4-trimethyl-4-phenyl-7-(pyridin-4-ylmethoxy)-1,2,3,4-tetrahydroquinolin-6-yl]-3,5-dichloro-benzamide

According to general procedure H, the compound described in example 28b (100 mg) 15 was alkylated with 4-picoly l chloride hydrochloride (36 mg) and Cs₂CO₃ (255 mg) in a mixture of DMF (1 ml) and CH₂Cl₂ (4 ml). The tile compound was obtained as the corresponding TFA salt after preparative HPLC (method A), followed by lyophilization.

Yield: 35 mg (TFA salt); MS-ESI: [M+H]⁺ = 588.4; HPLC: R_t = 18.0 min (method 2).

20 Example 29

N-[1-Acetyl-2,2,4-trimethyl-4-phenyl-7-(2-pyrrolidin-1-yl-ethoxy)-1,2,3,4-tetrahydroquinolin-6-yl]-3,5-dimethyl-benzamide

General procedure J: A mixture of the compound described in example 26b (100 mg), 2-chloroethylpyrrolidine hydrochloride (41 mg) and DIPEA (77 µl) in CH₂Cl₂ (5 ml) was stirred at room temperature until no more starting material remained. Water was added and the organic layer was separated, washed with brine, dried (MgSO₄) and concentrated *in vacuo*. Purification by means of preparative HPLC, followed by lyophilization gave the title compound as the corresponding TFA salt.

Yield: 104 mg (TFA salt); MS-ESI: $[M+H]^+$ = 554.4; HPLC: R_t = 15.2 min (method 2).

Example 30

N-[1-Acetyl-2,2,4-trimethyl-7-(5-methyl-isoxazol-3-ylmethoxy)-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dimethyl-benzamide

- 5 According to general procedure J, the compound described in example 26b (100 mg) was alkylated with (chloromethyl)-5-methylisooxazole (32 mg) and DIPEA (77 μ l) in CH_2Cl_2 (5 ml). Purification by means of preparative HPLC (method A), followed by lyophilization gave the title compound.

Yield: 41 mg; MS-ESI: $[M+H]^+$ = 552.4; HPLC: R_t = 31.3 min (method 2).

10 **Example 31**

N-[1-Acetyl-7-(2-diethylamino-ethoxy)-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl]-3,5-dimethyl-benzamide; compound with trifluoro-acetic acid

- According to general procedure J, the compound described in example 26b (100 mg) was alkylated with *N,N*-diethylaminoethylchloride hydrochloride (42 mg) and DIPEA (77 μ l) in CH_2Cl_2 (5 ml). Purification by means of preparative HPLC (method A), followed by lyophilization gave the title compound as its corresponding TFA salt.

Yield: 43 mg (TFA salt); MS-ESI: $[M+H]^+$ = 556.4; HPLC: R_t = 15.2 min (method 2).

Example 32

- 20 *N-[1-Acetyl-2,2,4-trimethyl-4-phenyl-7-(pyridin-4-ylmethoxy)-1,2,3,4-tetrahydro-quinolin-6-yl]-5-bromo-2-methylamino-benzamide*

(a). *N-(1-Acetyl-7-methoxy-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)-5-bromo-2-methylamino-benzamide*

- According to general procedure F, the compound described in example 15e (1.0 g) was acylated with 5-bromo-2-methylamino-benzoyl chloride (1.43 g) in toluene (9 ml) and 25 pyridine (1 ml). The title compound was obtained by chromatography on silicagel using heptane/ethyl acetate = 8/2 (v/v) as the eluent.

Yield: 595 mg

(b). N-(1-Acetyl-7-hydroxy-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-5-bromo-2-methylamino-benzamide

- 5 According to general procedure G, the compound described in example 32a (595 mg) was stirred with AlCl_3 (0.75 g) in benzene (50 ml). The product obtained was used without further purification.

Yield: 437 mg

10 (c). N-[1-Acetyl-2,2,4-trimethyl-4-phenyl-7-(pyridin-4-ylmethoxy)-1,2,3,4-tetrahydro-quinolin-6-yl]-5-bromo-2-methylamino-benzamide

- According to general procedure H, the compound described in example 32b (44 mg) was alkylated with 4-picoly1 chloride hydrochloride (15 mg) and Cs_2CO_3 (ca 100 mg) in a mixture of DMF (1 ml) and CH_2Cl_2 (4 ml). The tile compound was obtained as the 15 corresponding TFA salt after preparative HPLC (method B).

Yield: 18 mg (TFA salt); MS-ESI: $[\text{M}+\text{H}]^+ = 629.4$; HPLC: $R_t = 18.1$ min (method 2).

Example 33

Furan-2-carboxylic acid (1-acetyl-7-dimethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

20 (a). (2,2,4-Trimethyl-1,2-dihydroquinolin-6-yl)-carbamic acid *tert*-butyl ester

- A mixture of *N*-Boc-1,4-phenylenediamine (75 g), MgSO_4 (216 g), 4-*tert*-butylcatechol (1.8 g) and iodine (4.7 g) in anhydrous acetone (600 ml) was refluxed for 20 h. The MgSO_4 was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was chromatographed on a short plug of silicagel using heptane/ethyl acetate = 25 8/2 (v/v) as the eluent to give the product as a brown oil.

Yield: 41 g.

(b). (1-Acetyl-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)-carbamic acid *tert*-butyl ester

- 30 A solution of the compound described in example 33a (41 g) in pyridine (200 ml) and CH_2Cl_2 (200 ml) was cooled to 0 °C. Acetyl chloride (21 ml) in CH_2Cl_2 (50 ml) was added dropwise. After complete addition the mixture was stirred for 3 h at room

temperature. Ethyl acetate (2 l) and H₂O (2 l) were added and the organic layer was separated, dried (MgSO₄) and concentrated *in vacuo*. The title compound was obtained by crystallization from ethyl acetate.

Yield: 23 g.

5

(c). 1-Acetyl-6-amino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline

According to general procedure G, the compound described in example 33b (33.3 g) was stirred with AlCl₃ (40.4 g) in benzene (700 ml). The product was purified by chromatography on silicagel using heptane/ethyl acetate = 8/2 (v/v) as the eluent.

10 Yield: 22.4 g

(d). (1-Acetyl-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-carbamic acid 9-fluorenylmethyl ester

Pyridine (6.4 ml) was added to a solution of the compound described in example 33c (22.4 g) in THF (300 ml) and the resulting mixture was cooled to 0 °C. A solution of FmocCl (20.7 g) in THF (100 ml) was added dropwise and after the addition was complete the mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated *in vacuo* and ethyl acetate (800 ml) and 0.3 M aq HCl (500 ml) were added. The organic layer was separated and washed with 0.3 M HCl (2×500 ml), H₂O (500 ml) and brine (500 ml), followed by drying (MgSO₄) and concentration *in vacuo*. The product was used without further purification in the next step.

20 Yield: 43 g

25 (e) (1-Acetyl-2,2,4-trimethyl-7-nitro-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-carbamic acid 9-fluorenylmethyl ester

Fuming nitric acid (3.07 ml) was added dropwise over a period of 10 min to a mixture of the compound described in example 33d (43 g) and acetic acid (230 ml) in CH₂Cl₂ (230 ml). The reaction mixture was stirred until full conversion of starting material after which H₂O (150 ml) was added. The aqueous layer was separated and extracted with CH₂Cl₂ (150 ml). The combined organic layers were washed with saturated aq NaHCO₃ (3×200 ml) and brine (200 ml), followed by drying over MgSO₄ and filtration. Methanol (ca 200 ml) was added and the CH₂Cl₂ was carefully removed *in*

vacuo, after which the mixture was allowed to stand at room temperature overnight. The bright yellow crystals were collected by filtration and dried ($MgSO_4$) *in vacuo*.

Yield: 29.3 g.

5 (f). (1-Acetyl-7-amino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-carbamic acid 9-fluorenylmethyl ester

According to general procedure E, the compound described in example 33e (20 g) was reduced using zinc dust (45 g) and acetic acid (20 ml) in THF (ca 600 ml), to give the product which was used crude in the next step.

10 Yield: 21 g

(g) (1-Acetyl-7-dimethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-carbamic acid 9-fluorenylmethyl ester

15 An aqueous solution of formaldehyde (37 %, 3.8 ml) was added to a solution of the compound described in example 33f (12 g), acetic acid (15.7 ml) and sodium cyanoborohydride (2.9 g) in methanol (200 ml), which gave rise to an exothermic reaction and the formation of a white precipitate. An additional amount of MeOH was added to facilitate stirring. After stirring for 15 min, the precipitate was collected by
20 filtration and washed with MeOH/H₂O = 1/1 (v/v). The filtrate was partly concentrated to give more solid material which was also collected. The combined solids were recrystallized from CH₂Cl₂/MeOH to give the dimethylated compound.

Yield: 9.7 g

25 (h). 1-Acetyl-6-Amino-7-dimethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinoline

Piperidine (7.7 ml) was added to a solution of the compound described in example 33g (4.5 g) in CH₂Cl₂ (70 ml). After 24 h, the reaction mixture was diluted with CH₂Cl₂ (100 ml) and washed with 0.5 M aq HCl (2×150 ml), water (100 ml) and brine (1 ml).
30 The organic layer was dried ($MgSO_4$) and diluted to a total volume of 200 ml. This stock solution of the title compound (ca 13.8 mg/ml) was used for further reactions.

(i). Furan-2-carboxylic acid (1-acetyl-7-dimethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

Triethylamine (38 μ l) and 2-furoyl chloride (27 μ l) were added to a solution of the compound described in example 33h (96.6 mg) in CH_2Cl_2 (10 ml) and the resulting mixture was stirred until full conversion of starting material was achieved. The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 \Rightarrow 0/1 (v/v) as the eluent.

Yield: 5.5 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 446.2$; HPLC: $R_t = 19.02$ min (method 2).

Example 34

10 5-Methyl-thiophene-2-carboxylic acid (1-acetyl-7-dimethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

According to general procedure A, the compound described in example 33h (96.6 mg) was acylated with 5-methylthiophene-2-carboxylic acid (39.1 mg), HATU (157 mg) and DIPEA (239 μ l) in CH_2Cl_2 (10 ml). The title compound was purified by preparative HPLC (method B).

Yield: 35.5 mg; MS-ESI: $[\text{M}+\text{H}]^+ = 476.2$; HPLC: $R_t = 21.26$ min (method 2).

Example 35

15 Biphenyl-4-carboxylic acid (1-acetyl-7-dimethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

According to general procedure A, the compound described in example 33h (96.6 mg) was acylated with 4-biphenylcarboxylic acid (54.4 mg), HATU (157 mg) and DIPEA (239 μ l) in CH_2Cl_2 (10 ml). The title compound was purified by preparative HPLC (method B).

Yield: 31.5 mg; MS-ESI: $[\text{M}+\text{H}]^+ = 532.4$; HPLC: $R_t = 24.92$ min (method 2).

25 **Example 36**

N-(1-Acetyl-7-dimethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-3,5-dibromo-benzamide

According to general procedure A, the compound described in example 33h (96.6 mg) was acylated with 3,5-dibromobenzoic acid (77 mg), HATU (157 mg) and DIPEA (239 μ l) in CH_2Cl_2 (10 ml). The title compound was purified by crystallization from $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$.

Yield: 24.3 mg; MS-ESI: $[M+H]^+$ = 614.2; HPLC: R_t = 27.71 min (method 2).

Example 37

Cyclopentanecarboxylic acid (1-acetyl-7-dimethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

- 5 According to general procedure A, the compound described in example 33h (137 mg) was acylated with cyclopentanecarboxylic acid (128 μ l), HATU (224 mg) and DIPEA (400 μ l) in CH_2Cl_2 (10 ml). The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

Yield: 148 mg; MS-ESI: $[M+H]^+$ = 448.4; HPLC: R_t = 12.93 min (method 1).

10 **Example 38**

N-(1-Acetyl-7-dimethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-isobutyramide

- According to general procedure A, the compound described in example 33h (137 mg) was acylated with isobutyric acid (110 μ l), HATU (224 mg) and DIPEA (400 μ l) in 15 CH_2Cl_2 (10 ml). The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent.

Yield: 43 mg; MS-ESI: $[M+H]^+$ = 422.4; HPLC: R_t = 9.99 min (method 1).

Example 39

Furan-2-carboxylic acid (1-acetyl-7-furan-2-ylcarbonylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-amide

- To solution of the compound described in example 33f (150 mg) and triethylamine (43 μ l) in CH_2Cl_2 (1 ml) was added 2-furoyl chloride (30 μ l). After complete consumption of starting material, 1 M aqueous HCl was added, the organic layer was separated followed by the addition of piperidine (1 ml) and the resulting mixture was stirred 25 overnight. The reaction mixture was washed with 1 M aqueous HCl, the organic layer separated, dried ($MgSO_4$) and concentrated *in vacuo*. The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 1/0 => 0/1 (v/v) as the eluent , followed by preparative HPLC (method A).

Yield: 18 mg; MS-ESI: $[M+H]^+$ = 512.4; HPLC: R_t = 19.92 min (method 2).

Example 40

5-Methyl-thiophene-2-carboxylic acid (1-acetyl-2,2,4-trimethyl-4-phenyl-7-propylamino-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

5 (a). 1-Acetyl-6-amino-2,2,4-trimethyl-4-phenyl-7-propylamino-1,2,3,4-tetrahydroquinoline

General procedure K: To a mixture of the compound described in example 33f (750 mg), acetic acid (953 µl), sodium cyanoborohydride (135 mg) and MeOH (10 ml) was added propionaldehyde (94.2 µl). The mixture was stirred for 18 h, water was added and the precipitate was collected by filtration. The precipitate was taken up in CH₂Cl₂ (10 ml), piperidine (1 ml) was added and the resulting mixture was stirred for 18 h. The reaction mixture was washed with 1 M aqueous HCl, the organic layer was separated and diluted to a total volume of 50 ml. This solution was used for following reactions.

10 (b). 5-Methyl-thiophene-2-carboxylic acid (1-acetyl-2,2,4-trimethyl-4-phenyl-7-propylamino-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

15 According to general procedure A, the compound described in example 40a (100 mg) was acylated with 5-methylthiophene-2-carboxylic acid (39.1 mg), HATU (157 mg) and DIPEA (239 µl) in CH₂Cl₂ (10 ml). The title compound was purified by preparative HPLC and lyophilized.

20 Yield: 18.3 mg; MS-ESI: [M+H]⁺ = 490.4; HPLC: R_t = 23.96 min (method 2).

Example 41

Biphenyl-4-carboxylic acid (1-acetyl-7-ethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

25 (a). 1-Acetyl-6-amino-7-ethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline

According to general procedure K, the compound described in example 33f (750 mg) was alkylated using acetaldehyde (73.3 µl), and deprotected with piperidine (1 ml) to give after work up and dilution a solution of the title compound in CH₂Cl₂.

30 (b). Biphenyl-4-carboxylic acid (1-acetyl-7-ethylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

According to general procedure A, the compound described in example 41a (100 mg) was acylated with 4-biphenylcarboxylic acid (54.4 mg), HATU (157 mg) and DIPEA (239 μ l) in CH_2Cl_2 (10 ml). The title compound was purified by preparative HPLC and lyophilized.

5 Yield: 9.8 mg; MS-ESI: $[\text{M}+\text{H}]^+ = 532.4$; HPLC: $R_t = 25.55$ min (method 2).

Example 42

5-Methyl-thiophene-2-carboxylic acid {1-acetyl-2,2,4-trimethyl-4-phenyl-7-[(pyridin-4-ylmethyl)-amino]-1,2,3,4-tetrahydro-quinolin-6-yl}-amide

10 (a). 1-Acetyl-6-amino-2,2,4-trimethyl-4-phenyl-7-[(pyridin-4-ylmethyl)-amino]-1,2,3,4-tetrahydroquinoline

According to general procedure K, the compound described in example 33f (750 mg) was alkylated using 4-pyridinecarboxaldehyde (125 μ l), and deprotected with piperidine (1 ml) to give after work up and dilution a solution of the title compound in CH_2Cl_2 .

15

(b). 5-Methyl-thiophene-2-carboxylic acid {1-acetyl-2,2,4-trimethyl-4-phenyl-7-[(pyridin-4-ylmethyl)-amino]-1,2,3,4-tetrahydro-quinolin-6-yl}-amide

20 According to general procedure A, the compound described in example 42a (114 mg) was acylated with 5-methylthiophene-2-carboxylic acid (39.1 mg), HATU (157 mg) and DIPEA (239 μ l) in CH_2Cl_2 (10 ml). The title compound was purified by preparative HPLC and lyophilized.

Yield: 51 mg; MS-ESI: $[\text{M}+\text{H}]^+ = 539.4$; HPLC: $R_t = 13.19$ min (method 2).

Example 43

5-Methyl-thiophene-2-carboxylic acid {1-acetyl-2,2,4-trimethyl-4-phenyl-7-[(pyridin-3-ylmethyl)-amino]-1,2,3,4-tetrahydro-quinolin-6-yl}-amide

(a). 1-Acetyl-6-amino-2,2,4-trimethyl-4-phenyl-7-[(pyridin-3-ylmethyl)-amino]-1,2,3,4-tetrahydroquinoline

30 According to general procedure K, the compound described in example 33f (750 mg) was alkylated using 3-pyridinecarboxaldehyde (125 μ l), and deprotected with piperidine (1 ml) to give after work up and dilution a solution of the title compound in CH_2Cl_2 .

(b). 5-Methyl-thiophene-2-carboxylic acid {1-acetyl-2,2,4-trimethyl-4-phenyl-7-[(pyridin-3-ylmethyl)-amino]-1,2,3,4-tetrahydro-quinolin-6-yl}-amide

According to general procedure A, the compound described in example 43a (114 mg) was acylated with 5-methylthiophene-2-carboxylic acid (39.1 mg), HATU (157 mg) 5 and DIPEA (239 μ l) in CH_2Cl_2 (10 ml). The title compound was purified by preparative HPLC and lyophilized.

Yield: 44 mg; MS-ESI: $[\text{M}+\text{H}]^+ = 539.4$; HPLC: $R_t = 13.45$ min (method 2).

Example 44

10 *N*-(1-Acetyl-7-isobutylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-3,5-dibromo-benzamide

(a). 1-Acetyl-6-amino-7-isobutylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline

According to general procedure K, the compound described in example 33f (750 mg) was alkylated isobutyraldehyde (119 μ l), and deprotected with piperidine (1 ml) to give 15 after work up and dilution a solution of the title compound in CH_2Cl_2 .

(b). *N*-(1-Acetyl-7-isobutylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-3,5-dibromo-benzamide

According to general procedure A, the compound described in example 44a (114 mg) 20 was acylated with 3,5-dibromobenzoic acid (77 mg), HATU (157 mg) and DIPEA (239 μ l) in CH_2Cl_2 (10 ml). The title compound was purified by preparative HPLC and lyophilized.

Yield: 54 mg; MS-ESI: $[\text{M}+\text{H}]^+ = 642.4$; HPLC: $R_t = 29.47$ min (method 2).

Example 45

Biphenyl-4-carboxylic acid (1-acetyl-7-benzylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

- 5 (a). 1-Acetyl-6-amino-7-benzylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline

According to general procedure K, the compound described in example 33f (750 mg) was alkylated using benzaldehyde (133 µl), and deprotected with piperidine (1 ml) to give after work up and dilution a solution of the title compound in CH₂Cl₂.

- 10 (b). Biphenyl-4-carboxylic acid (1-acetyl-7-benzylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

15 According to general procedure A, the compound described in example 45a (113 mg) was acylated with 4-biphenylcarboxylic acid (54.4 mg), HATU (157 mg) and DIPEA (239 µl) in CH₂Cl₂ (10 ml). The title compound was purified by preparative HPLC and lyophilized.

Yield: 114 mg; MS-ESI: [M+H]⁺ = 594.4; HPLC: R_t = 26.46 min (method 2).

Example 46

5-Methyl-thiophene-2-carboxylic acid (1-acetyl-7-benzylamino-2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

- 20 According to general procedure A, the compound described in example 45a (113 mg) was acylated with 5-methylthiophene-2-carboxylic acid (39.1 mg), HATU (157 mg) and DIPEA (239 µl) in CH₂Cl₂ (10 ml). The title compound was purified by preparative HPLC and lyophilized.

Yield: 107 mg; MS-ESI: [M+H]⁺ = 538.4; HPLC: R_t = 18.59 min (method 2).

25 **Example 47**

N-{1-Acetyl-2,2,4-trimethyl-4-phenyl-7-[(pyridin-3-ylmethyl)-amino]-1,2,3,4-tetrahydro-quinolin-6-yl}-3,5-dibromo-benzamide

- 30 According to general procedure A, the compound described in example 43a (114 mg) was acylated with 3,5-dibromobenzoic acid (77 mg), HATU (157 mg) and DIPEA (239 µl) in CH₂Cl₂ (10 ml). The title compound was purified by preparative HPLC and lyophilized.

Yield: 41 mg; MS-ESI: $[M+H]^+$ = 677.2; HPLC: R_t = 14.88 min (method 2).

Example 48

N-(1-Acetyl-7-dimethylamino-4-methyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-3,5-dibromo-benzamide

5 (a). 4-Methyl-1,2-dihydroquinoline

A solution of lepidine (10.0 g) in THF was cooled down to -78°C , after which a solution of $\text{BH}_3\cdot\text{THF}$ in THF (1 M, 70 ml) was added. After 2 h, a solution of sodium bis(2-methoxy-ethoxy)aluminum dihydride in toluene (3.5 M, 40 ml) was added and the reaction mixture was stirred for an additional 2 h. Water was added and the mixture 10 diluted with ethyl acetate. The organic layer was separated, dried (MgSO_4) and partially concentrated *in vacuo* causing crystallization of the title compound. The crystals were collected by filtration to yield 3.5 g after drying *in vacuo*. The remaining mother liquor was concentrated *in vacuo* and the residue was purified by chromatography on silicagel using heptane/ethyl acetate = 0/1 => 1/0 (v/v) as the 15 eluent to give an additional 4.4 g of the title compound.

Yield: 7.9 g.

(b). 1-Acetyl-4-methyl-1,2-dihydroquinoline

According to general procedure C, the compound described in example 48a (7.9 g) was 20 acylated with acetyl chloride (11.8 ml) and DMA (34 ml) in CH_2Cl_2 (50 ml) at 0°C . The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 6/4 as the eluent.

Yield: 8.8 g

25 (c). 1-Acetyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline

According to general procedure G, the compound described in example 48b (8.8 g) was stirred with AlCl_3 (18.8 g) in benzene (250 ml). The product obtained was used without further purification.

Yield: 12.0 g

30

(d). 1-Acetyl-4-methyl-6-nitro-4-phenyl-1,2,3,4-tetrahydroquinoline

To a solution of the compound described in example 48c (5.0 g) and acetic anhydride (189 μ l) in CH_2Cl_2 (50 ml) was added dropwise fuming HNO_3 (9.4 ml). After the reaction was complete, water was added and the organic layer was washed with brine, separated and concentrated *in vacuo*. The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 6/4 (v/v) as the eluent.

Yield: 3.86 g

(e). 1-Acetyl-6-amino-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline

According to general procedure E, the compound described in example 48d (3.86 g) was reduced using zinc dust (16 g) and acetic acid (7 ml) in THF (ca 250 ml), to give the product which was used crude in the next step.

Yield: 2.2 g

(f). (1-Acetyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-carbamic acid 9-fluorenylmethyl ester

Pyridine (314 μ l) was added to a solution of the compound described in example 48e (1.0 g) in THF (10 ml) and the resulting mixture was cooled to 0 °C. FmocCl (1.01 g) was added and the mixture was stirred for 18 h at room temperature, after which time the reaction mixture was concentrated *in vacuo*. The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 6/4 (v/v) as the eluent.

Yield: 950 mg

(g). (1-Acetyl-4-methyl-7-nitro-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-carbamic acid 9-fluorenylmethyl ester

To a solution of the compound described in example 48f (850 mg) and acetic anhydride (17 μ l) in CH_2Cl_2 (5 ml) was added dropwise fuming HNO_3 (842 μ l). After the reaction was complete, water was added and the organic layer was washed with brine, separated and concentrated *in vacuo*. The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 9/1 => 0/1 (v/v) as the eluent.

Yield: 714 mg

(h). (1-Acetyl-7-amino-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-carbamic acid 9-fluorenylmethyl ester

According to general procedure E, the compound described in example 48g (2.37 g) was reduced using zinc dust (5.6 g) and acetic acid (2.4 ml) in THF (ca 50 ml), to give
5 the product which was used crude in the next step.

Yield: 2.66 g

(i). (1-Acetyl-7-dimethylamino-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-6-yl)-carbamic acid 9-fluorenylmethyl ester

10 An aqueous solution of formaldehyde (37 %, 650 µl) was added to a solution of the compound described in example 48h (2.66 g), acetic acid (3.1 ml) and sodium cyanoborohydride (232 mg) in methanol (50 ml), and the resulting mixture was stirred for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was taken up in ethyl acetate and washed with water and brine. The organic layer was separated,
15 dried ($MgSO_4$) and concentrated *in vacuo*. The title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 9/1 => 0/1 (v/v) as the eluent.

Yield: 1.0 g

20 (j). 1-Acetyl-6-amino-7-dimethylamino-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline
Piperidine (1.8 ml) was added to a solution of the compound described in example 48i (1 g) in CH_2Cl_2 (20 ml) and the mixture was stirred until no more starting material remained. The reaction mixture was concentrated *in vacuo*, and the title compound was purified by chromatography on silicagel using heptane/ethyl acetate = 9/1 => 0/1 (v/v)
25 as the eluent.

Yield: 370 mg.

(k). *N*-(1-Acetyl-7-dimethylamino-4-methyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-3,5-dibromo-benzamide

30 According to general procedure A, the compound described in example 48j (74 mg) was acylated with 3,5-dibromobenzoic acid (70 mg), HATU (131 mg) and DIPEA (120 µl) in CH_2Cl_2 (3 ml). The title compound was purified by preparative HPLC and lyophilized.

Yield: 82 mg; MS-ESI: $[M+H]^+$ = 586.2; HPLC: R_t = 22.40 min (method 2).

Example 49

5-Bromo-thiophene-2-carboxylic acid (1-acetyl-7-dimethylamino-4-methyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

- 5 According to general procedure A, the compound described in example 48j (74 mg) was acylated 5-bromothiophene-2-carboxylic acid (52 mg), HATU (131 mg) and DIPEA (120 μ l) in CH_2Cl_2 (3 ml). The title compound was purified by preparative HPLC and lyophilized.

Yield: 69 mg; MS-ESI: $[M+H]^+$ = 514.2; HPLC: R_t = 17.01 min (method 2).

10 Example 50

5-Chloro-thiophene-2-carboxylic acid (1-acetyl-7-dimethylamino-4-methyl-4-phenyl-1,2,3,4-tetrahydro-quinolin-6-yl)-amide

- According to general procedure A, the compound described in example 48j (74 mg) was acylated 5-chlorothiophene-2-carboxylic acid (52 mg), HATU (131 mg) and 15 DIPEA (120 μ l) in CH_2Cl_2 (3 ml). The title compound was purified by preparative HPLC and lyophilized.

Yield: 81 mg; MS-ESI: $[M+H]^+$ = 468.2; HPLC: R_t = 17.49 min (method 2).

Example 51

CHO-FSH *in vitro* bioactivity

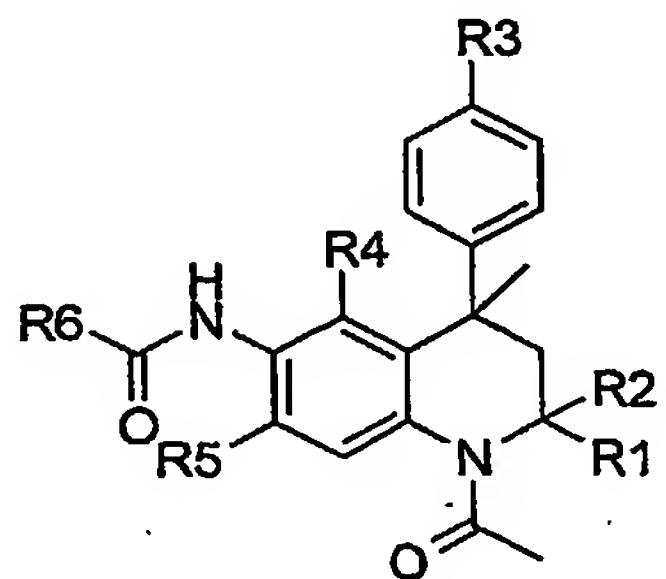
- 20 FSH activity of compounds were tested in Chinese Hamster Ovary (CHO) cells stably transfected with the human FSH receptor and cotransfected with a cAMP responsive element (CRE) / promotor directing the expression of a firefly luciferase reporter gene. Binding of ligand to the Gs-coupled FSH receptor will result in an increase of cAMP, which in turn will induce an increased transactivation of the luciferase reporter construct. To test antagonistic properties recombinant FSH in a concentration that induces approximately 80% of the maximal stimulation of cAMP accumulation in the 25 absence of test compound was added (rec-hFSH, 10mU/ml). The luciferase signal was quantified using a luminescence counter. For test compounds, EC₅₀ values (concentration of test compound causing half-maximal (50 %) stimulation or reduction)

were calculated. For that purpose the software program GraphPad PRISM, version 3.0 (GraphPad software Inc., San Diego) was used.

Compounds of all examples exhibited an EC₅₀ (IC₅₀) value of less than 10⁻⁵ M in either an agonistic or antagonistic assay set-up or both. The compounds of examples 5-8, 10-
5 14, 16, 18-20, 33-35, 37, 38, 41 and 45-50 showed an EC₅₀ of less than 10⁻⁷ M in at least one of the assays.

Claims

1. A tetrahydroquinoline derivative according to Formula 1,



Formula I

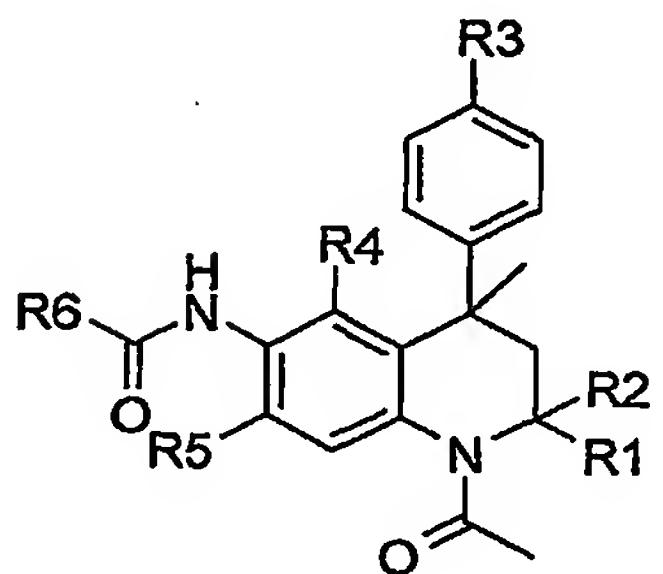
5 or a pharmaceutically acceptable salt thereof, wherein
R¹ and R² are H or Me
R³ is H, hydroxy, (1-4C)alkoxy, (di)(1-4C)alkylamino(2-4C)alkoxy or (2-
6)heterocycloalkyl(2-4C)alkoxy
R⁴ is H, OH, (1-4C)alkoxy or R⁷
10 R⁵ is H, OH, (1-4C)alkoxy or R⁷
with the proviso that if R⁴ is H, R⁵ is not H, OH or (1-4C)alkoxy and that if R⁵ is
H, R⁴ is not H, OH or (1-4C)alkoxy
R⁶ is (2-5C)heteroaryl, (6C)aryl, (3-8C)cycloalkyl, (2-6C)heterocycloalkyl or (1-
6C)alkyl
15 R⁷ is amino, (di)(1-4C)alkylamino, (6C)arylcarbonylamino,
(6C)arylcarbonyloxy, (2-5C)heteroarylcarbonylamino, (2-
5C)heteroarylcarbonyloxy, R⁸-(2-4C)alkylamino, R⁸-(2-4C)alkoxy, R⁹-
methylamino or R⁹-methoxy
R⁸ is hydroxy, amino, (1-4C)alkoxy, (di)(1-4C)alkylamino, (2-
20 6C)heterocycloalkyl, (2-6C)heterocycloalkylcarbonylamino, (di)(1-
4C)alkylaminocarbonylamino, (1-4C)alkoxycarbonylamino and
R⁹ is aminocarbonyl, (di)(1-4C)alkylaminocarbonyl, (2-5C)heteroaryl or
(6C)aryl.

2. The tetrahydroquinoline derivative of claim 1 wherein R⁶ is (2-5C)heteroaryl, (6C)aryl, (3-8C)cycloalkyl or (1-6C)alkyl.
3. The tetrahydroquinoline derivative of claims 1 or 2 wherein R⁷ is (di)(1-4C)alkylamino, (2-5C)heteroarylcarbonyloxy, R⁸-(2-4C)alkoxy, R⁹-methylamino or R⁹-methoxy.
5
4. The tetrahydroquinoline derivative of claims 1-3 wherein R⁸ is amino, (di)(1-4C)alkylamino, (2-6C)heterocycloalkyl or (2-6C)heterocycloalkylcarbonylamino.
5. The tetrahydroquinoline derivative of claims 1-4 wherein R⁷ is (di)(1-4C)alkylamino, R⁸-(2-4C)alkoxy, R⁹-methylamino or R⁹-methoxy
10
6. The tetrahydroquinoline derivative of claims 1-5 wherein R⁸ is amino, (di)(1-4C)alkylamino or (2-6C)heterocycloalkyl.
7. The tetrahydroquinoline derivative of claims 1-6 wherein R⁸ is (di)(1-4C)alkylamino or (2-6C)heterocycloalkyl.
- 15 8. The tetrahydroquinoline derivative of claims 1-7 wherein R⁷ is (di)(1-4C)alkylamino, R⁸-(2-4C)alkoxy, R⁹-methylamino or R⁹-methoxy.
9. The tetrahydroquinoline derivative of claims 1-8 wherein R⁶ is (2-5C)heteroaryl or (6C)aryl.
10. The tetrahydroquinoline derivative of claims 1-9 wherein R⁶ is (4-5C)heteroaryl
20 or (6C)aryl and R9 is aminocarbonyl, (di)(1-4C)alkylaminocarbonyl, (3-5C)heteroaryl or (6C)aryl.
11. The tetrahydroquinoline derivative of claims 1-10 wherein R⁷ is (di)(1-4C)alkylamino, R⁸-ethoxy, R⁹-methylamino or R⁹-methoxy and R⁹ is aminocarbonyl, (di)(1-4C)alkylaminocarbonyl, (3-5C)heteroaryl or (6C)aryl
25
12. The tetrahydroquinoline derivative of claims 1-11 wherein R⁸ is, (di)(1-4C)alkylamino, (4-5C)heterocycloalkyl and R⁹ is aminocarbonyl, (di)(1-4C)alkylaminocarbonyl, (3-5C)heteroaryl or (6C)aryl.
13. A pharmaceutical composition comprising the tetrahydroquinoline derivative of any one of claims 1-12 and pharmaceutically suitable auxiliaries.
- 30 14. The tetrahydroquinoline derivative of claims 1-12 for use in therapy.

15. Use of the tetrahydroquinoline derivative of any one of claims 1-12 or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for fertility regulation.

Abstract

The present invention relates to tetrahydroquinoline derivatives having general formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein R¹ and R² are H or Me; R³ is H, hydroxy, (1-4C)alkoxy, (di)(1-4C)alkylamino(2-4C)alkoxy or (2-6)heterocycloalkyl(2-4C)alkoxy; R⁴ is H, OH, (1-4C)alkoxy or R⁷; R⁵ is H, OH, (1-4C)alkoxy or R⁷, with the proviso that if R⁴ is H, R⁵ is not H, OH or (1-4C)alkoxy and that if R⁵ is H, R⁴ is not H, OH or (1-4C)alkoxy; R⁶ is (2-5C)heteroaryl, (6C)aryl, (3-8C)cycloalkyl, (2-6C)heterocycloalkyl or (1-6C)alkyl; R⁷ is amino, (di)(1-4C)alkylamino, (6C)arylcarbonylamino, (6C)arylcarbonyloxy, (2-5C)heteroarylcarbonylamino, (2-5C)heteroarylcarbonyloxy, R⁸-(2-4C)alkylamino, R⁸-(2-4C)alkoxy, R⁹-methylamino or R⁹-methoxy; R⁸ is hydroxy, amino, (1-4C)alkoxy, (di)(1-4C)alkylamino, (2-6C)heterocycloalkyl, (2-6C)heterocycloalkylcarbonylamino, (di)(1-4C)alkylaminocarbonylamino, (1-4C)alkoxycarbonylamino and R⁹ is aminocarbonyl, (di)(1-4C)alkylaminocarbonyl, (2-5C)heteroaryl or (6C)aryl.

The present invention also relates to pharmaceutical compositions comprising said derivatives and the use of these derivatives to regulate fertility.